

10/679,478

STN-Structure Search
11/29/07

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L7 ANSWER 1 OF 26 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2007:912224 CAPLUS
DOCUMENT NUMBER: 147:269196
TITLE: Methods for inhibition of lymphangiogenesis and tumor metastasis
INVENTOR(S): Varner, Judith A.; Garmy-Susini, Barbara
PATENT ASSIGNEE(S): The Regents of the University of California, USA
SOURCE: PCT Int. Appl., 90pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|------|----------|-----------------|----------|
| WO 2007092471 | A2 | 20070816 | WO 2007-US3205 | 20070205 |
| W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW | | | | |
| RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM | | | | |

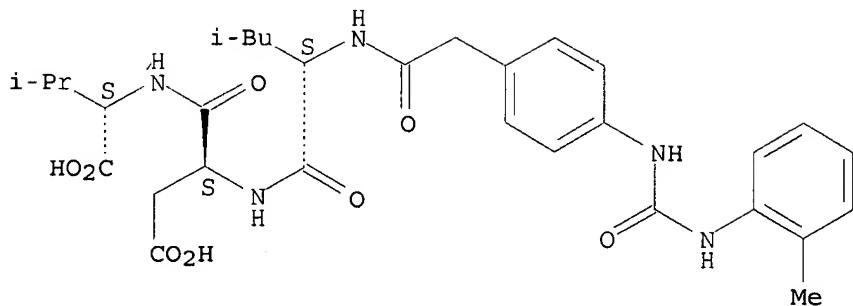
PRIORITY APPLN. INFO.: US 2006-765068P P 20060203
AB The present invention is directed to compns. and methods for inhibiting the development of new lymphatic vessels, and for inhibiting tumor cell dissemination through the lymphatics. In preferred embodiments, the present invention utilizes agents that inhibit the specific binding of integrin $\alpha 4\beta 1$ ($\alpha 4\beta 1$, VLA-4) to one or more of its ligands. The invention further relates to methods for screening test compds. for their ability to inhibit undesirable lymphangiogenesis and/or tumor metastasis.

IT 181520-66-1 181520-85-4 187735-94-0
187737-40-2
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(inhibition of lymphangiogenesis and tumor metastasis)

RN 181520-66-1 CAPLUS
CN 1,3-Benzodioxole-5-propanoic acid, β -[[[(2S)-4-methyl-1-oxo-2-[[[4-[(phenylamino)carbonyl]amino]phenyl]acetyl]amino]pentyl]amino]-, (β S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

Absolute stereochemistry.



L7 ANSWER 2 OF 26 CAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 2007:560477 CAPLUS

TITLE: Effect of enalapril on the in vitro and in vivo peptidyl cleavage of a potent VLA-4 antagonist

AUTHOR(S): Karanam, B. V.; Jayraj, A.; Rabe, M.; Wang, Z.; Keohane, C.; Strauss, J.; Vincent, S.

CORPORATE SOURCE: Department of Drug Metabolism, Merck Research Laboratories, Rahway, NJ. 07065. USA

Xenobiotica (2007), 37(5), 487-502

CODEN: XENOBH ISSN: 0049-8254

PUBLISHER: Informa Healthcare

DOCUMENT TYPE: Journal

LANGUAGE: English

AB BIO1211 is a small peptidyl potent antagonist of the activated form of $\alpha\beta 1$ integrin. The effect of enalapril on the in vitro and in vivo cleavage of BIO1211 was investigated. In heparinized blood, plasma and rat liver, lung and intestinal homogenates, BIO1211 was converted rapidly to BIO1588 by hydrolytic cleavage of the terminal dipeptide moiety. This cleavage could be inhibited by EDTA and the ACE inhibitor, enalaprilat, the de-esterified acid derivative of enalapril. Enalaprilat inhibited the hydrolysis of BIO1211 in a concentration-dependent manner with

IC50

values of 2 nM in human and sheep plasma and 10 nM in rat plasma. In rat lung homogenate supernatant, the maximum inhibition of the conversion of BIO1211 to BIO1588 was .apprx.80% at 1 μ M with no further effect up to 100 μ M of enalaprilat. Following a concomitant IV administration of enalapril and BIO1211 at 3 mg/kg each, the AUC and the half-life values of BIO1211 increased 18- and 10-fold, resp. The AUC of BIO1588 decreased .apprx.2-fold with no change in its plasma half-life. When rats were dosed i.v. with enalapril followed by an intratracheal dose of BIO1211, there was .apprx.2.5-fold decrease in the AUC of BIO1588 and a 2.4-fold increase in its plasma half-life.

IT INDEXING IN PROGRESS

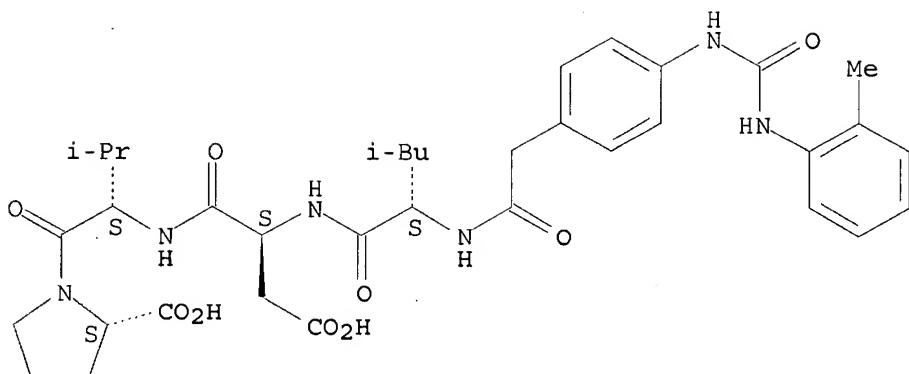
IT 187735-94-0, BIO1211

RL: PKT (Pharmacokinetics); BIOL (Biological study)
(enalapril effect on peptidyl cleavage of VLA-4 antagonist BIO1211)

RN 187735-94-0 CAPLUS

CN L-Proline, N-[2-[4-[[[[(2-methylphenyl)amino]carbonyl]amino]phenyl]acetyl]-L-leucyl-L- α -aspartyl-L-valyl- (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 19 THERE ARE 19 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 3 OF 26 CAPLUS COPYRIGHT 2007 ACS on STN
 ACCESSION NUMBER: 2006:1292873 CAPLUS
 DOCUMENT NUMBER: 146:206619
 TITLE: Structure-activity relationship studies of a series of peptidomimetic ligands for $\alpha 4\beta 1$ integrin on Jurkat T-leukemia cells
 AUTHOR(S): Liu, Ruiwu; Peng, Li; Han, Huijun; Lam, Kit S.
 CORPORATE SOURCE: Division of Hematology and Oncology, Department of Internal Medicine, UC Davis Cancer Center, University of California Davis, Sacramento, CA, 95817, USA
 SOURCE: Biopolymers (2006), 84(6), 595-604
 CODEN: BIPMAA; ISSN: 0006-3525
 PUBLISHER: John Wiley & Sons, Inc.
 DOCUMENT TYPE: Journal
 LANGUAGE: English
 OTHER SOURCE(S): CASREACT 146:206619
 GI

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

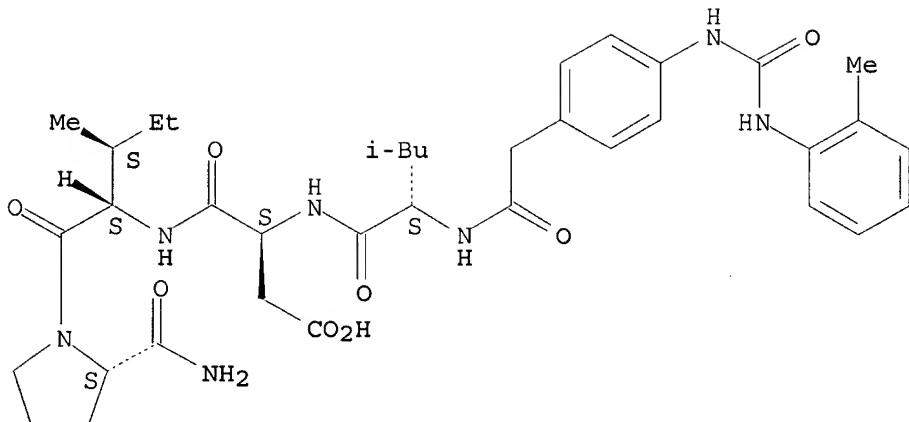
AB $\alpha 4\beta 1$ Integrin is a therapeutic target for inflammation, autoimmune diseases, and lymphoid cancers. A series of peptidomimetic ligands based on the Nle-D-I motif have been synthesized and their binding affinities (IC50) to activated $\alpha 4\beta 1$ integrin on Jurkat T-leukemia cells were determined using a cell adhesion assay. One of the 51 ligands, peptide I, has an IC50 = 0.6 nM, more than two fold increase of binding affinity than the initial lead compound II. Extensive SAR studies provided important information for further ligand optimization, which has served as a foundation for studies that ultimately led to identification of a potent ligand with an IC50 = 2 pM.

IT 922716-39-0P
 RL: PAC (Pharmacological activity); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
 (solid-phase preparation and structure-activity relationships of peptides as ligands of $\alpha 4\beta 1$ integrin)

RN 922716-39-0 CAPLUS

CN L-Prolinamide, N-[2-[4-[[[(2-methylphenyl)amino]carbonyl]amino]phenyl]acetyl]-L-leucyl-L- α -aspartyl-L-isoleucyl- (CA INDEX NAME)

Absolute stereochemistry.



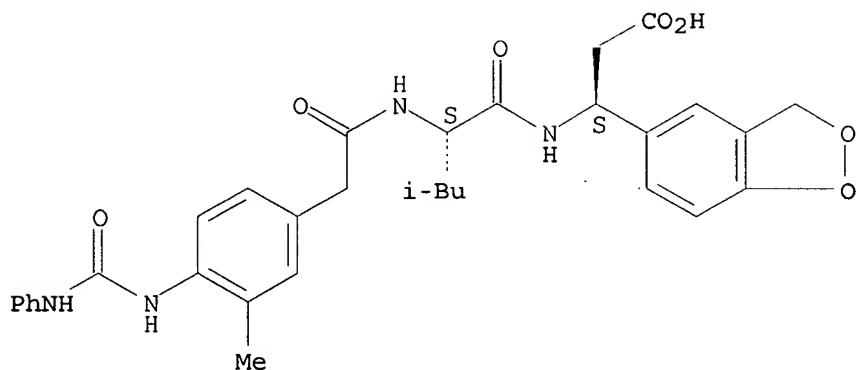
REFERENCE COUNT: 18 THERE ARE 18 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE REFORMAT.

L7 ANSWER 4 OF 26 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2005:324277 CAPLUS
DOCUMENT NUMBER: 142:390938
TITLE: Anti-integrin $\alpha 4\beta 1$ antibodies and ligands
for altering hematopoietic progenitor cell adhesion,
differentiation, and migration
INVENTOR(S): Varner, Judith A.
PATENT ASSIGNEE(S): The Regents of the University of California, USA
SOURCE: PCT Int. Appl., 122 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|--|------|----------|-----------------|------------|
| WO 2005033275 | A2 | 20050414 | WO 2004-US31825 | 20040928 |
| WO 2005033275 | A3 | 20070104 | | |
| W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW | | | | |
| RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW; AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG | | | | |
| AU 2004278748 | A1 | 20050414 | AU 2004-278748 | 20040928 |
| CA 2545248 | A1 | 20050414 | CA 2004-2545248 | 20040928 |
| EP 1685236 | A2 | 20060802 | EP 2004-789173 | 20040928 |
| R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, PL, SK, HR | | | | |
| JP 2007509042 | T | 20070412 | JP 2006-534024 | 20040928 |
| IRITY APPLN. INFO.: | | | US 2003-507202P | P 20030929 |
| | | | WO 2004-US31825 | W 20040928 |

AB The present invention satisfies the need in the art by providing methods for altering hematopoietic progenitor cell adhesion and/or migration to a target tissue. The target tissue is an injured, ischemic and/or malignant vascular endothelium, muscle, neuron, tumor, peripheral blood, cord blood,

Absolute stereochemistry.



L7 ANSWER 5 OF 26 CAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 2005:86537 CAPLUS

DOCUMENT NUMBER: 143:431977

TITLE: Identified a morpholinyl-4-piperidinylacetic acid derivative as a potent oral active VLA-4 antagonist. [Erratum to document cited in CA142:085870]

AUTHOR(S): Chiba, Jun; Machinaga, Nobuo; Takashi, Tohru; Ejima, Akio; Takayama, Gensuke; Yokoyama, Mika; Nakayama, Atsushi; Baldwin, John J.; McDonald, Edward; Moriarty, Kevin J.; Sarko, Christopher R.; Saionz, Kurt W.; Swanson, Robert; Hussain, Zahid; Wong, Angela Medicinal Chemistry Research Laboratory, Daiichi Pharmaceutical Co., Ltd., Edogawa-ku, Tokyo, 134-8630, Japan

CORPORATE SOURCE: Medicinal Chemistry Research Laboratory, Daiichi Pharmaceutical Co., Ltd., Edogawa-ku, Tokyo, 134-8630, Japan

SOURCE: Bioorganic & Medicinal Chemistry Letters (2005), 15 (4), 1259

CODEN: BMCLE8; ISSN: 0960-894X
PUBLISHER: Elsevier B.V.

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Kevin J. Moriarty and Christopher R. Sarko are added as the tenth and eleventh authors; they are both affiliated with Pharmacopeia Drug Discovery, Inc., Princeton, New Jersey, USA. The correct author list is given.

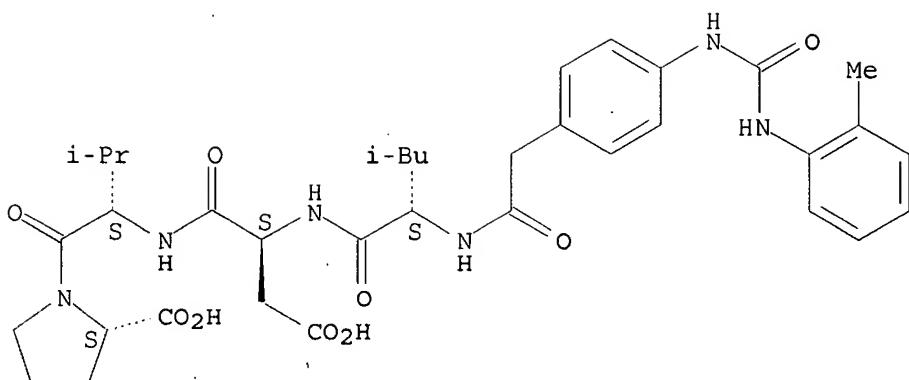
IT 187735-94-0, Bio-1211

RL: PAC (Pharmacological activity); BIOL (Biological study)
(morpholinyl-4-piperidinylacetic acid derivative as potent oral active VLA-4 antagonist (Erratum))

RN 187735-94-0 CAPLUS

CN L-Proline, N-[2-[4-[[[(2-methylphenyl)amino]carbonyl]amino]phenyl]acetyl]-L-leucyl-L- α -aspartyl-L-valyl- (CA INDEX NAME)

Absolute stereochemistry.



L7 ANSWER 6 OF 26 CAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 2004:1068245 CAPLUS

DOCUMENT NUMBER: 142:85870

TITLE: Identified a morpholinyl-4-piperidinylacetic acid derivative as a potent oral active VLA-4 antagonist
 Chiba, Jun; Machinaga, Nobuo; Takashi, Tohru; Ejima, Akio; Takayama, Gensuke; Yokoyama, Mika; Nakayama, Atsushi; Baldwin, John J.; McDonald, Edward; Saionz, Kurt W.; Swanson, Robert; Hussain, Zahid; Wong, Angela
 Medicinal Chemistry Research Laboratory, Daiichi Pharmaceutical Co., Ltd., Edogawa-ku, Tokyo, 134-8630, Japan

AUTHOR(S):

CORPORATE SOURCE:

SOURCE: Bioorganic & Medicinal Chemistry Letters (2005), 15(1), 41-45

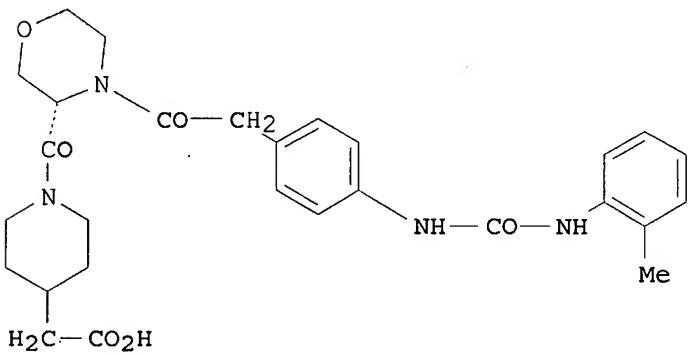
PUBLISHER: Elsevier B.V.

DOCUMENT TYPE: Journal

LANGUAGE: English

OTHER SOURCE(S): CASREACT 142:85870

GI



I

AB An investigation into the structure-activity relationship of a lead compound, prolyl-5-aminopentanoic acid, led to the identification of a novel series of 4-piperidinylacetic acid, 1-piperazinylacetic acid, and 4-aminobenzoic acid derivs. as potent VLA-4 antagonists with low nanomolar

IC50 values. A representative compound morpholinyl-4-piperidinylacetic acid derivative (I: IC50 = 4.4 nM) showed efficacy in the Ascaris antigen-sensitized murine airway inflammation model by oral administration.

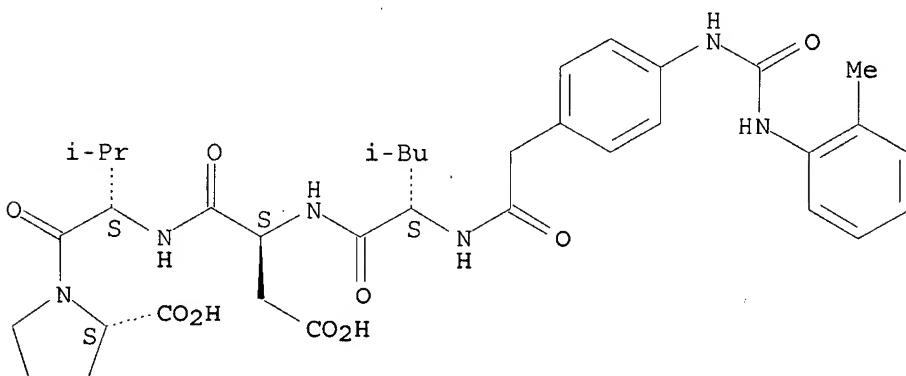
IT 187735-94-0, Bio-1211

RL: PAC (Pharmacological activity); BIOL (Biological study)
(morpholinyl-4-piperidinylacetic acid derivative as potent oral active VLA-4 antagonist)

RN 187735-94-0 CAPLUS

CN L-Proline, N-[2-[4-[[[(2-methylphenyl)amino]carbonyl]amino]phenyl]acetyl]-L-leucyl-L- α -aspartyl-L-valyl- (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 24 THERE ARE 24 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 7 OF 26 CAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 2004:1019870 CAPLUS

DOCUMENT NUMBER: 142:677

TITLE: Ig Fc fragment-linked biologically active molecules for the inhibition of drug binding to serum albumin

INVENTOR(S): Bitonti, Alan J.; Palombella, Vito J.; Stattel, James M.; Peters, Robert T.

PATENT ASSIGNEE(S): Syntonix Pharmaceuticals, Inc., USA

SOURCE: PCT Int. Appl., 75 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

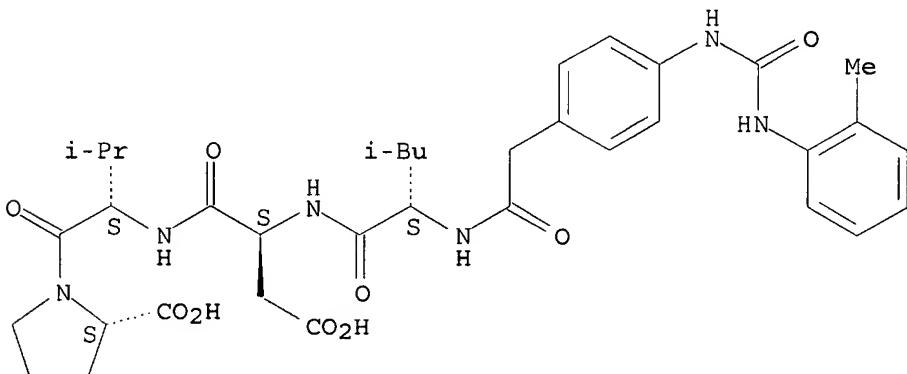
| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|------|----------|-----------------|----------|
| WO 2004100882 | A2 | 20041125 | WO 2004-US14065 | 20040506 |
| WO 2004100882 | A3 | 20070531 | | |
| W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW | | | | |
| RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, AP, EA, EP, OA | | | | |

| | | | |
|--|-------------|-----------------|------------|
| AU 2004238263 | A1 20041125 | AU 2004-238263 | 20040506 |
| CA 2522690 | A1 20041125 | CA 2004-2522690 | 20040506 |
| US 2005037947 | A1 20050217 | US 2004-841949 | 20040506 |
| EP 1624846 | A2 20060215 | EP 2004-751454 | 20040506 |
| R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, PL, SK, HR | | | |
| PRIORITY APPLN. INFO.: | | US 2003-469603P | P 20030506 |
| | | WO 2004-US14065 | W 20040506 |

AB The invention relates to improved therapeutics for treating diseases or conditions that provide greater bioavailability and more predictable dosing. The invention relates to a chimeric protein comprised of a biol. active mol. linked to an Fc fragment of an Ig, wherein the chimeric protein binds less serum albumin compared to the same biol. active mol. of the chimeric protein not linked to an Fc fragment of an Ig. The invention also relates to a method of treating a disease or condition, the method comprising administering a chimeric protein comprising a biol. active mol. linked to an Fc fragment of an Ig, wherein the chimeric protein binds less serum albumin compared to the same biol. active mol. of the chimeric protein not linked to an Fc fragment of an Ig. Compound preparation (e.g. SYN00534-Fc) is included.

IT 187735-94-0, Bio 1211
 RL: PKT (Pharmacokinetics); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
 (Ig Fc fragment-linked biol. active mols. for inhibition of drug binding to serum albumin)
 RN 187735-94-0 CAPLUS
 CN L-Proline, N-[2-[4-[[[(2-methylphenyl)amino]carbonyl]amino]phenyl]acetyl]-L-leucyl-L- α -aspartyl-L-valyl- (CA INDEX NAME)

Absolute stereochemistry.



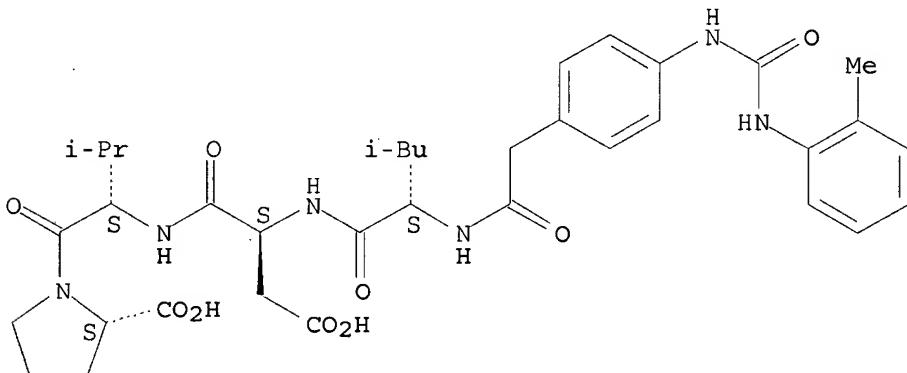
L7 ANSWER 8 OF 26 CAPLUS COPYRIGHT 2007 ACS on STN
 ACCESSION NUMBER: 2004:582909 CAPLUS
 DOCUMENT NUMBER: 141:218310
 TITLE: Insights into Phenylalanine Derivatives Recognition of VLA-4 Integrin: From a Pharmacophoric Study to 3D-QSAR and Molecular Docking Analyses
 AUTHOR(S): Macchiarulo, Antonio; Costantino, Gabriele; Meniconi, Mirco; Pleban, Karin; Ecker, Gerhard; Bellocchi, Daniele; Pellicciari, Roberto
 CORPORATE SOURCE: Dipartimento di Chimica e Tecnologia del Farmaco, Universita di Perugia, Perugia, 06127, Italy
 SOURCE: Journal of Chemical Information and Computer Sciences (2004), 44(5), 1829-1839
 CODEN: JCISD8; ISSN: 0095-2338
 PUBLISHER: American Chemical Society

DOCUMENT TYPE: Journal
 LANGUAGE: English

AB The very late antigen-4 (VLA-4), also known as integrin $\alpha 4\beta 1$, is expressed on monocytes, T- and B-lymphocytes, basophils, and eosinophils and is involved in the massive recruitment of granulocytes in different pathol. conditions such as multiple sclerosis and asthma. VLA-4 interacts with its endogenous ligand VCAM-1 during chronic inflammation, and blockade of VLA-4 /VCAM-1 interaction is a potential target for immunosuppression. Two classes of VLA-4 antagonists have so far been reported: β -amino acid derivs. containing a diaryl urea moiety (BIO-1211) and phenylalanine derivs. (TR-14035). With the aim of clarifying the structural basis responsible for VLA-4 recognition by phenylalanine derivs., the authors developed a combined computational study on a set of 128 antagonists available through the literature. Our computational approach is composed of three parts. (i) A VCAM-1 based pharmacophore was constructed with a restricted number of phenylalanine derivs. to identify the region of the protein that resembles synthetic antagonists. The pharmacophore was instrumental in constructing an alignment of a set of 128 compds. This alignment was exploited to build a pseudoreceptor model with the RECEPTOR program. (ii) 3D-QSAR anal. was carried out on the computed electrostatic and steric interaction energies with the pseudoreceptor surface. The 3D-QSAR anal. yielded a predictive model able to explain much of the variance of the 128 antagonists. (iii) A homol. modeling study of the headpiece of VLA-4 based on the crystal structure of $\alpha\beta 3$ was performed. Docking expts. of TR-14035 into the binding site of VLA-4 aided the interpretation of the 3D-QSAR model. The obtained results will be fruitful for the design of new potent and selective antagonists of VLA-4.

IT 187735-94-0, Bio-1211
 RL: PAC (Pharmacological activity); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
 (3D-QSAR and mol. docking analyses of phenylalanine derivs. recognition of VLA-4 integrin)
 RN 187735-94-0 CAPLUS
 CN L-Proline, N-[2-[4-[[[(2-methylphenyl)amino]carbonyl]amino]phenyl]acetyl]-L-leucyl-L- α -aspartyl-L-valyl- (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 47 THERE ARE 47 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 9 OF 26 CAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 2004:559787 CAPLUS

DOCUMENT NUMBER: 142:68815

TITLE: Effects of BIO-1211 on eosinophil chemotaxis, recruitment and mediator release

AUTHOR(S): Zhao, Xiaoyan; Chen, Jiqiang; Xie, Qiangmin; Tang, Huifang; Bian, Rulian

CORPORATE SOURCE: Zhejiang Respiratory Drugs Research Laboratory of State Food and Drug Administration of China, College of Medicine, Zhejiang University, Hangzhou, 310031, Peop. Rep. China

SOURCE: Zhejiang Daxue Xuebao, Yixueban (2003), 32(4), 279-282, 291

CODEN: ZDXYA9; ISSN: 1008-9292

PUBLISHER: Zhejiang Daxue Chubanshe

DOCUMENT TYPE: Journal

LANGUAGE: Chinese

AB The effects of very late antigen (VLA) antagonist BIO-1211 on eosinophil chemotaxis, recruitment and mediator release are studied. Eosinophil chemotaxis was induced by platelet activating factor (PAF) in vitro, and eosinophil recruitment and release were determined in vivo. VLA antagonist BIO-1211 inhibits eosinophil chemotaxis induced by PAF. The inhibitory rates at 4×10^{-11} , 4×10^{-10} , 4×10^{-9} mol/L are 24.9, 29.9 and 31.3%, resp. Pretreatment by BIO-1211 (1, 3 and 10 mg/kg, i.p.) inhibited the recruitment of eosinophils in PAF in sephadex induced rat in a dose-dependent manner, and the inhibitory rates are 60.3, 68.9 and 72.9%, resp. BIO-1211 can not inhibit eosinophil peroxidase (EPO) release from eosinophils. BIO-1211 inhibits eosinophil chemotaxis and recruitment, and alleviates local inflammation, and may represent a new type of drug for allergic diseases.

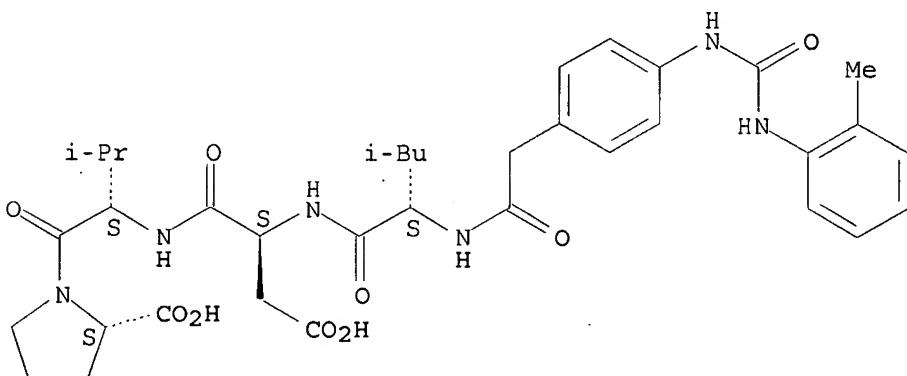
IT 187735-94-0, BIO-1211

RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(effects of BIO-1211 on eosinophil chemotaxis, recruitment and mediator release)

RN 187735-94-0 CAPLUS

CN L-Proline, N-[2-[4-[[[(2-methylphenyl)amino]carbonyl]amino]phenyl]acetyl]-L-leucyl-L- α -aspartyl-L-valyl- (CA INDEX NAME)

Absolute stereochemistry.



L7 ANSWER 10 OF 26 CAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 2004:559785 CAPLUS

DOCUMENT NUMBER: 142:253303

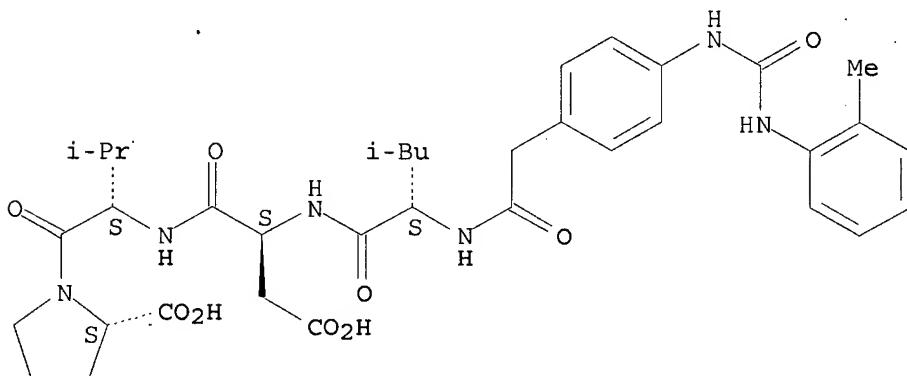
TITLE: Research on the mechanism of asthma and the development of new drugs

AUTHOR(S): Chen, Jiqiang; Bian, Rulian

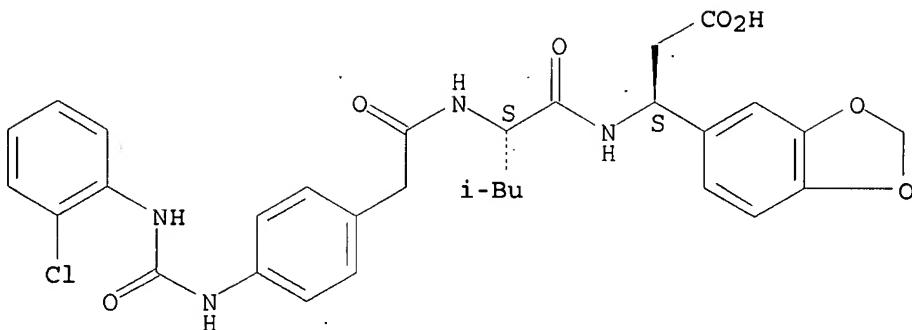
CORPORATE SOURCE: Zhejiang Respiratory Drugs Research Laboratory of State, Food and Drug Administration of China, College of Medicine, Zhejiang University, Hangzhou, 310031, Peop. Rep. China

SOURCE: Zhejiang Daxue Xuebao, Yixueban (2003), 32(4), 269-273
 CODEN: ZDXYA9; ISSN: 1008-9292
 PUBLISHER: Zhejiang Daxue Chubanshe
 DOCUMENT TYPE: Journal; General Review
 LANGUAGE: Chinese
 AB A review with 27 refs. on the mechanism of asthma and the development of new drugs with emphases on asthma as chronic airway inflammation and the development of new drugs including ciclamilast, BIO-1211 and a chinese medicine composed of polysaccharides from cryptoporus volvatus.
 IT 187735-94-0, BIO-1211
 RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
 (research on mechanism of asthma and the development of new drugs)
 RN 187735-94-0 CAPLUS
 CN L-Proline, N-[2-[4-[[[(2-methylphenyl)amino]carbonyl]amino]phenyl]acetyl]-L-leucyl-L- α -aspartyl-L-valyl- (CA INDEX NAME)

Absolute stereochemistry.



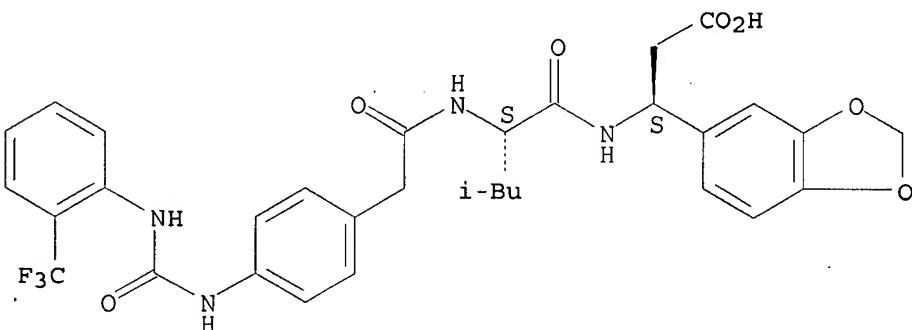
L7 ANSWER 11 OF 26 CAPLUS COPYRIGHT 2007 ACS on STN
 ACCESSION NUMBER: 2002:813789 CAPLUS
 DOCUMENT NUMBER: 138:280734
 TITLE: 3D QSAR (COMFA) of a series of potent and highly selective VLA-4 antagonists
 AUTHOR(S): Singh, Juswinder; Van Vlijmen, Herman; Lee, Wen-Cherng; Liao, Yusheng; Lin, Ko-Chung; Ateeq, Humayun; Cuervo, Julio; Zimmerman, Craig; Hammond, Charles; Karpusas, Michael; Palmer, Rex; Chattopadhyay, Tapan; Adams, Steven P.
 CORPORATE SOURCE: Biogen Inc, Cambridge, MA, 02142, USA
 SOURCE: Journal of Computer-Aided Molecular Design (2002), 16(3), 201-211
 CODEN: JCADEQ; ISSN: 0920-654X
 PUBLISHER: Kluwer Academic Publishers
 DOCUMENT TYPE: Journal
 LANGUAGE: English
 AB The integrin VLA-4 ($\alpha 4\beta 1$) is involved in the migration of white blood cells to sites of inflammation, and is implicated in the pathol. of a variety of diseases including asthma and multiple sclerosis. We report the structure-activity relationships of a series of VLA-4 antagonists that were based upon the integrin-binding sequence of the connecting segment peptide of fibronectin (Leu-Asp-Val), and of VCAM-1 (Ile-Asp-Ser), both natural ligands of VLA-4. We explore variation in the ligand derived peptide portion of these antagonists and also in the novel N-terminal cap, which have discovered through chemical optimization, and which confers high affinity and selectivity. Using the x-ray derived conformation of the



RN 505082-16-6 CAPLUS

CN β -Alanine, N-[4-[[[2-(trifluoromethyl)phenyl]amino]carbonyl]amino]p-phenyl]acetyl]-L-leucyl-3-(1,3-benzodioxol-5-yl)-, (3S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT:

26 THERE ARE 26 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 12 OF 26 CAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 2002:434328 CAPLUS

DOCUMENT NUMBER: 137:163322

TITLE: Identification of Potent and Novel $\alpha 4\beta 1$ Antagonists Using in Silico Screening

AUTHOR(S): Singh, Juswinder; van Vlijmen, Herman; Liao, Yusheng; Lee, Wen-Cherng; Cornebise, Mark; Harris, Mary; Shu, I-hsiang; Gill, Alan; Cuervo, Julio H.; Abraham, William M.; Adams, Steven P.

CORPORATE SOURCE: Department of Drug Design and Evaluation, Biogen Inc., Cambridge, MA, 02142, USA

SOURCE: Journal of Medicinal Chemistry (2002), 45(14), 2988-2993

PUBLISHER: CODEN: JMCMAR; ISSN: 0022-2623
American Chemical Society

DOCUMENT TYPE: Journal

LANGUAGE: English

OTHER SOURCE(S): CASREACT 137:163322

AB The antigen $\alpha 4\beta 1$ (very late antigen-4, VLA-4) plays an important role in the migration of white blood cells to sites of inflammation. It has been implicated in the pathol. of a variety of diseases including asthma, multiple sclerosis, and rheumatoid arthritis. The authors describe a series of potent inhibitors of $\alpha 4\beta 1$ that were discovered using computational screening for replacements of the peptide region of an existing tetrapeptide-based $\alpha 4\beta 1$ inhibitor

(4- [N' - (2-methylphenyl)ureido] phenylacetyl-Leu-Asp-Val) (I) derived from fibronectin. The search query was constructed using a model of I that was based upon the x-ray conformation of the related integrin-binding region of vascular cell adhesion mol.-1 (VCAM-1). The 3D search query consisted of the N-terminal cap and the carboxyl side chain of I because, upon the basis of existing structure-activity data on this series, these were known to be critical for high-affinity binding to $\alpha 4\beta 1$. The computational screen identified 12 reagents from a virtual library of 8624 mols. as satisfying the model and the authors synthetic filters. All of the synthesized compds. tested inhibit $\alpha 4\beta 1$ association with VCAM-1, with the most potent compound having an IC50 of 1 nM, comparable to the starting compound. Using CATALYST, a 3D QSAR was generated that rationalizes the variation in activities of these $\alpha 4\beta 1$ antagonists. The most potent compound was evaluated in a sheep model of asthma, and a 30 mg nebulized dose was able to inhibit early and late airway responses in allergic sheep following antigen challenge and prevented the development of nonspecific airway hyperresponsiveness to carbachol. Our results demonstrate that it is possible to rapidly identify nonpeptidic replacements of integrin peptide antagonists. This approach should be useful in identification of nonpeptidic $\alpha 4\beta 1$ inhibitors with improved pharmacokinetic properties relative to their peptidic counterparts.

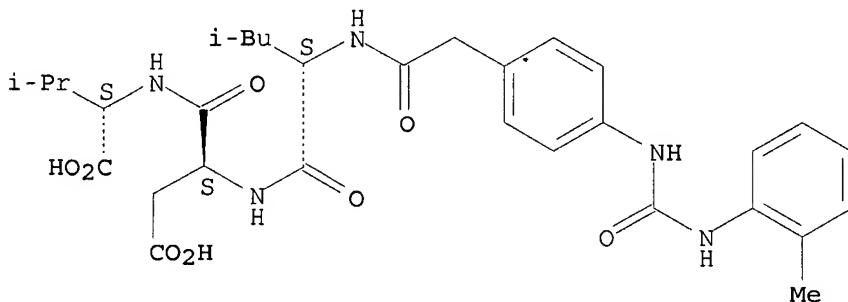
IT 187737-40-2

RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(identification of potent and novel $\alpha 4\beta 1$ antagonists using in silico screening in relation to asthma treatment)

RN 187737-40-2 CAPLUS

CN L-Valine, N-[2- [4- [[[(2-methylphenyl)amino]carbonyl]amino]phenyl]acetyl] -L-leucyl-L- α -aspartyl- (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 15 THERE ARE 15 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 13 OF 26 CAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 2002:336120 CAPLUS

DOCUMENT NUMBER: 137:288800

TITLE: Pulmonary eosinophilia in a murine model of allergic inflammation is attenuated by small molecule $\alpha 4\beta 1$ antagonists

AUTHOR(S): Kudlacz, E.; Whitney, C.; Andresen, C.; Duplantier, A.; Beckius, G.; Chupak, L.; Klein, A.; Kraus, K.; Milici, A.

CORPORATE SOURCE: Pfizer Global Research and Development, Groton, CT, USA

SOURCE: Journal of Pharmacology and Experimental Therapeutics (2002), 301(2), 747-752

CODEN: JPETAB; ISSN: 0022-3565

PUBLISHER: American Society for Pharmacology and Experimental Therapeutics

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Inhibition of $\alpha 4\beta 1$ /vascular cell adhesion mol.-1 (VCAM-1) interactions have therapeutic potential in treating allergic airway disease because of the importance of these adhesion mols. in the trafficking of eosinophils, lymphocytes, and monocytes. The authors examined several small mol. inhibitors of $\alpha 4\beta 1$ /VCAM-1 interactions with in vitro potencies (IC50 values) ranging from 0.52 nM (CP-664511; 3-[3-(1-{2-[3-methoxy-4-(3-O-tolyl-ureido)phenyl]-acetylamino}-3-methyl-butyl)isoxazol-5-yl]-propionic acid) to 38.5 nM (CP-609643; 3-[3-(3-methyl-1-{2-[4-(3-O-tolyl-ureido)-phenyl]-acetylamino}-butyl)-isoxazol-5-yl]-propionic acid). The same compds. were evaluated in vivo using a murine model of ovalbumin-induced pulmonary eosinophilia. In this model, systemic administration of antibodies against $\alpha 4$ reduced bronchoalveolar lavage (BAL) eosinophilia .apprx.60%. Small mol. $\alpha 4\beta 1$ antagonists were administered by intratracheal instillation and demonstrated dose-dependent inhibition of BAL eosinophil nos. and achieved a maximum inhibition of .apprx.60%. In general, the rank order of potency for these compds. in vitro was consistent with that observed in vivo, which confirms that their efficacy is likely via blockade of $\alpha 4\beta 1$ /VCAM-1 interactions. The most potent compound, CP-664511, also inhibited BAL eosinophilia following s.c. administration (1-10 mg/kg, s.c.). These data support the utility of small mol. $\alpha 4\beta 1$ antagonists in the treatment of relevant diseases, such as asthma.

IT 187735-94-0, BIO1211

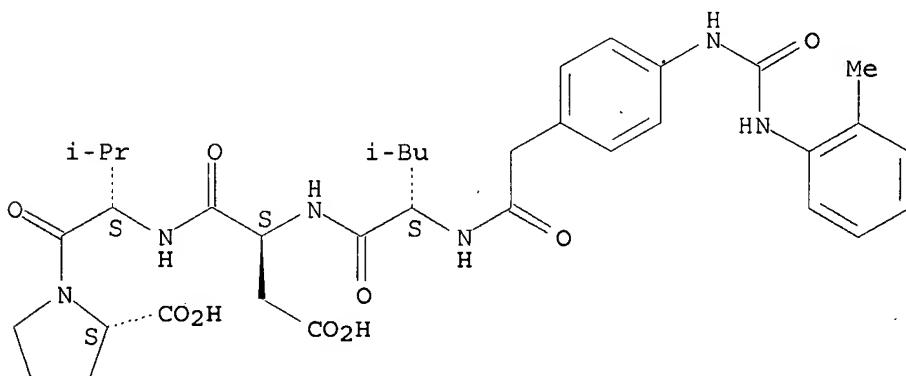
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(pulmonary eosinophilia in murine model of allergic inflammation is attenuated by small mol. $\alpha 4\beta 1$ antagonists)

RN 187735-94-0 CAPLUS

CN L-Proline, N-[2-[4-[[[(2-methylphenyl)amino]carbonyl]amino]phenyl]acetyl]-L-leucyl-L- α -aspartyl-L-valyl- (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT:

39

THERE ARE 39 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

Answers
L7 ANSWER 14 OF 26 CAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 2002:312019 CAPLUS

DOCUMENT NUMBER: 136:325828

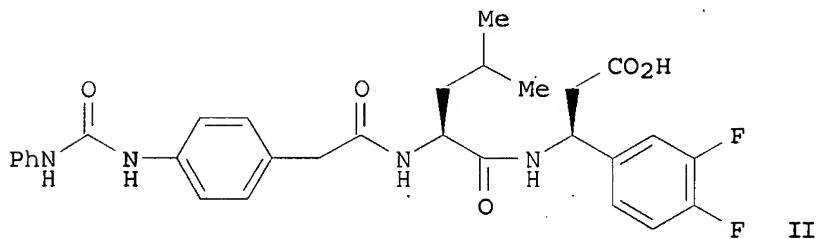
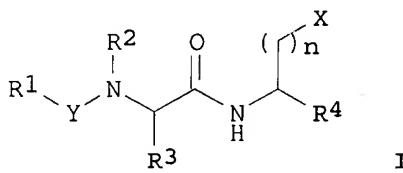
TITLE: Preparation of dipeptide derivatives as cell adhesion inhibitors

INVENTOR(S): Adams, Steven P.; Lin, Ko-Chung; Lee, Wen-Cherng; Castro, Alfredo C.; Zimmerman, Craig N.; Hammond,

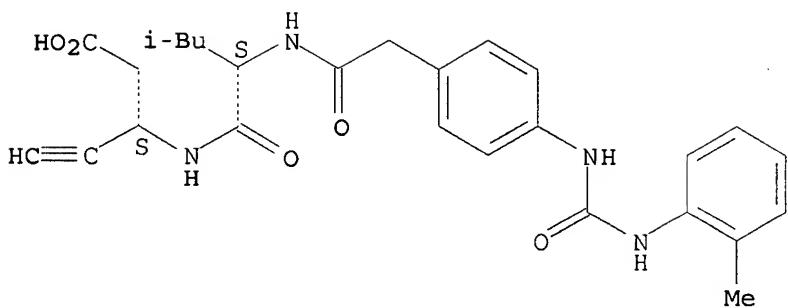
Charles E.; Liao, Yu-Sheng; Cuervo, Julio Hernan
Singh, Juswinder
PATENT ASSIGNEE(S): Biogen, Inc., USA
SOURCE: U.S., 50 pp., Cont.-in-part of U.S. 6,306,840.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|------|----------|-----------------|-------------|
| US 6376538 | B1 | 20020423 | US 1997-875321 | 19970919 |
| US 6306840 | B1 | 20011023 | US 1995-376372 | 19950123 |
| WO 9622966 | A1 | 19960801 | WO 1996-US1349 | 19960118 |
| W: AL, AM, AT, AU, AZ, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI | | | | |
| RW: KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE | | | | |
| EP 1142867 | A2 | 20011010 | EP 2001-107877 | 19960118 |
| R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI | | | | |
| AU 766538 | B2 | 20031016 | AU 2000-62432 | 20001002 |
| US 2003018016 | A1 | 20030123 | US 2001-2341 | 20011023 |
| US 6630512 | B2 | 20031007 | | |
| US 7001921 | B1 | 20060221 | US 2003-625626 | 20030724 |
| US 2006166866 | A1 | 20060727 | US 2003-679478 | 20031007 |
| PRIORITY APPLN. INFO.: | | | | |
| | | | US 1995-376372 | A2 19950123 |
| | | | WO 1996-US1349 | W 19960118 |
| | | | AU 1996-49115 | A3 19960118 |
| | | | EP 1996-905316 | A3 19960118 |
| | | | US 1997-875321 | A3 19970919 |
| | | | US 2001-935461 | A1 20010822 |
| | | | US 2001-2341 | A1 20011023 |

OTHER SOURCE(S): MARPAT 136:325828
GI



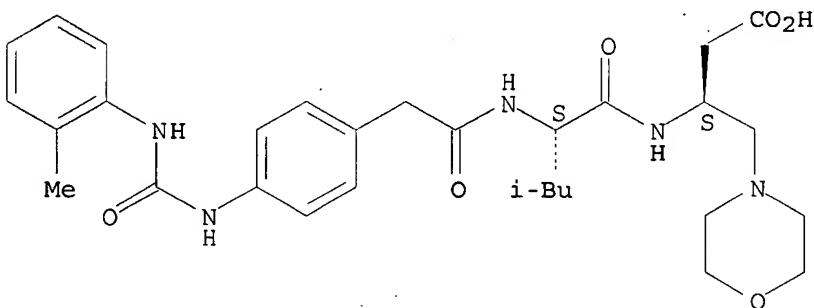
AB Novel dipeptide analogs I [X = CO₂H, PO₃H-, SO₂R₅, SO₃H, OPO₃H-, CO₂R₄; Y = CO, SO₂, PO₂; n = 0-2; R₁ = optionally substituted alkyl, alkenyl, alkynyl, aryl-fused cycloalkyl, cycloalkenyl, aryl, aralkyl, aralkenyl,



RN 181523-75-1 CAPLUS

CN 4-Morpholinebutanoic acid, β -[[[(2S)-4-methyl-2-[[[4-[[[(2-methylphenyl)amino]carbonyl]amino]phenyl]acetyl]amino]-1-oxopentyl]amino], (BS) - (9CI) (CA INDEX NAME)

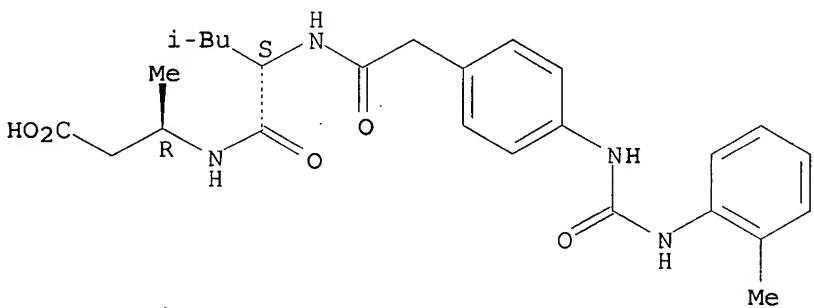
Absolute stereochemistry.



RN 181525-87-1 CAPLUS

CN Butanoic acid, 3-[[[(2S)-4-methyl-2-[[[4-[[[(2-methylphenyl)amino]carbonyl]amino]phenyl]acetyl]amino]-1-oxopentyl]amino], (3R) - (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT:

39

THERE ARE 39 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 15 OF 26 CAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 2001:780025 CAPLUS

DOCUMENT NUMBER: 136:232102

TITLE: Design and Synthesis of Potent and Selective Inhibitors of Integrin VLA-4

AUTHOR(S): Wattanasin, Sompong; Weidmann, Beat; Roche, Didier;

Myers, Stewart; Xing, Amy; Guo, Qin; Sabio, Michael;
von Matt, Peter; Hugo, Ronald; Maida, Susan; Lake,
Philip; Weetall, Marla

CORPORATE SOURCE: Novartis Pharmaceuticals Corporation, Novartis
Institute for Biomedical Research, Summit, NJ, 07901,
USA

SOURCE: Bioorganic & Medicinal Chemistry Letters (2001),
11(22), 2955-2958

CODEN: BMCLE8; ISSN: 0960-894X
Elsevier Science Ltd.

PUBLISHER: Journal

DOCUMENT TYPE: Journal

LANGUAGE: English

OTHER SOURCE(S): CASREACT 136:232102

AB The synthesis and identification of a novel series of inhibitors of integrin VLA-4 are described. Their in vitro activity and selectivity against closely related integrins are also presented. The compds. prepared and tested were modeled upon (βS) - β -[(2S)-4-methyl-2-[[4-[[[(2-methylphenyl)amino]carbonyl]amino]phenyl]acetyl]amino]-1-oxopentyl]amino]-1,3-benzodioxole-5-propanoic acid and $(3R)$ -3-[(2S)-4-methyl-2-[[3-[[[(2-methylphenyl)amino]carbonyl]amino]phenyl]acetyl]amino]-1-oxopentyl]amino]-5-hexenoic acid.

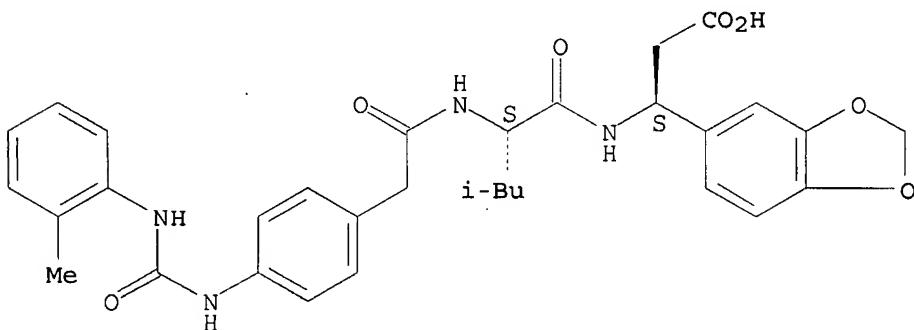
IT 181522-44-1

RL: PAC (Pharmacological activity); BIOL (Biological study)
(design and synthesis of selective integrin VLA-4 inhibitors)

RN 181522-44-1 CAPLUS

CN 1,3-Benzodioxole-5-propanoic acid, β -[(2S)-4-methyl-2-[[4-[[[(2-methylphenyl)amino]carbonyl]amino]phenyl]acetyl]amino]-1-oxopentyl]amino]-, (βS) - (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 26 THERE ARE 26 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 16 OF 26 CAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 2001:771942 CAPLUS

DOCUMENT NUMBER: 136:226237

TITLE: LC/MS/MS plasma assay for the peptidomimetic VLA4 antagonist I and its major active metabolite II: for treatment of asthma by inhalation

AUTHOR(S): Fisher, Alison L.; DePuy, Elizabeth; Jayaraj, Andrew;
Raab, Conrad; Braun, Matt; Ellis-Hutchings, Michel;
Zhang, Jin; Rogers, John D.; Musson, Donald G.

CORPORATE SOURCE: WP75A-303, Merck Research Laboratories, West Point,
PA, 19486, USA

SOURCE: Journal of Pharmaceutical and Biomedical Analysis
(2002), 27(1-2), 57-71

CODEN: JPBADA; ISSN: 0731-7085
Elsevier Science B.V.

DOCUMENT TYPE: Journal
 LANGUAGE: English

AB In vitro and in animals, I is a potent and specific peptidomimetic for the potential treatment of airway inflammation in the pathogenesis of asthma. Preclin. studies indicated extensive conversion of I to an active metabolite II, and thus, a very sensitive assay for I and II was needed to support an inhalation ascending-dose study in man. The LC/MS/MS plasma/urine assay method (1.0 mL of sample) involves the following: liquid-liquid extraction of acidified plasma into pentane-EtOAc (90:10 volume/volume); evaporation of the organic extract, reconstitution into MeOH; addition of H₂O to the methanolic extract and freezing. After thawing, the extract is centrifuged and the clear supernatant injected for chromatog. Extract is chromatographed on a YMC ODS-AM column (50+2.0 mm). For detection, a Sciex 365 LC/MS/MS with an electrospray inlet and used in the pos. ion, multiple reaction monitoring mode was used to monitor precursor fragment ions of m/z 709,594 for I and m/z 513,380 for II. The plasma assay was linear over the concentration range of 0.1-100 ng/mL in plasma for I and II. Accuracy and precision for I ranged from 97.9 to 102.1% of nominal with a 0.84-10.65% CV; similarly for II, 98.0-101.7% and 1.39-9.28% CV, resp. Extraction recovery averaged 63.7% for I and 64.9% for II. This general assay methodol. may be applied to assay small acidic peptides and peptidomimetics from biol. fluids by LC/MS/MS.

IT 187735-94-0 224577-01-9

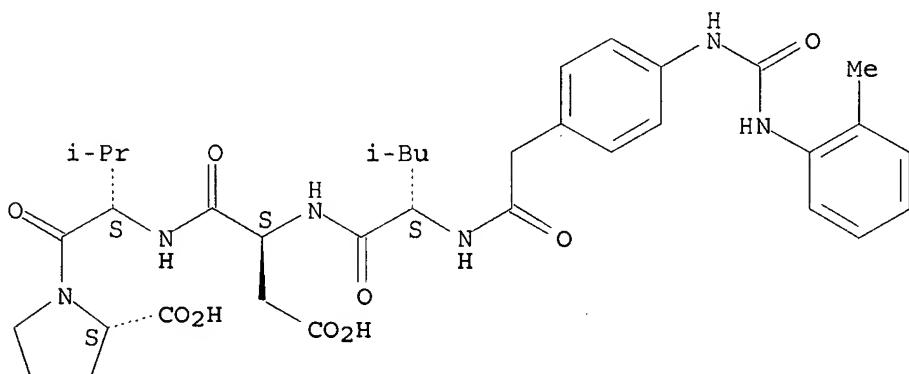
RL: ANT (Analyte); ANST (Analytical study)

(LC/MS/MS plasma assay for the peptidomimetic VLA4 antagonist I and its major active metabolite II: for treatment of asthma by inhalation)

RN 187735-94-0 CAPLUS

CN L-Proline, N-[2-[4-[[[(2-methylphenyl)amino]carbonyl]amino]phenyl]acetyl]-L-leucyl-L- α -aspartyl-L-valyl- (CA INDEX NAME)

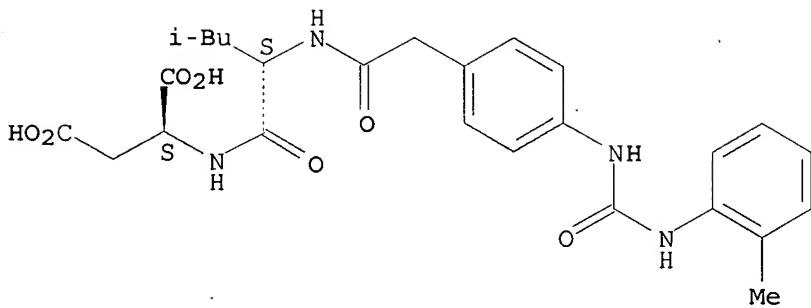
Absolute stereochemistry.



RN 224577-01-9 CAPLUS

CN L-Aspartic acid, N-[[4-[[[(2-methylphenyl)amino]carbonyl]amino]phenyl]acet yl]-L-leucyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 17 OF 26 CAPLUS COPYRIGHT 2007 ACS on STN
 ACCESSION NUMBER: 2001:137020 CAPLUS
 DOCUMENT NUMBER: 134:193741
 TITLE: Preparation of peptide derivatives as cell adhesion inhibitors
 INVENTOR(S): Lee, Wen-Cherng; Scott, Daniel; Cornebise, Mark; Petter, Russell
 PATENT ASSIGNEE(S): Biogen, Inc., USA
 SOURCE: PCT Int. Appl., 144 pp.
 CODEN: PIXXD2
 DOCUMENT TYPE: Patent
 LANGUAGE: English
 FAMILY ACC. NUM. COUNT: 1
 PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|------|----------|------------------|----------|
| WO 2001012186 | A1 | 20010222 | WO 2000-US22285, | 20000814 |
| W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG | | | | |
| CA 2380817 | A1 | 20010222 | CA 2000-2380817 | 20000814 |
| BR 2000013248 | A | 20020723 | BR 2000-13248 | 20000814 |
| HU 2002002469 | A2 | 20021128 | HU 2002-2469 | 20000814 |
| EP 1265606 | A1 | 20021218 | EP 2000-959232 | 20000814 |
| EP 1265606 | B1 | 20061025 | | |
| R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL | | | | |
| JP 2003506491 | T | 20030218 | JP 2001-516532 | 20000814 |
| EE 200200070 | A | 20030415 | EE 2002-70 | 20000814 |
| US 6630503 | B1 | 20031007 | US 2000-638652 | 20000814 |
| NZ 517011 | A | 20040227 | NZ 2000-517011 | 20000814 |
| AU 780610 | B2 | 20050407 | AU 2000-70586 | 20000814 |
| AT 343383 | T | 20061115 | AT 2000-959232 | 20000814 |
| EP 1741428 | A2 | 20070110 | EP 2006-21333 | 20000814 |
| EP 1741428 | A3 | 20070509 | | |
| R: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LI, LU, MC, NL, PT, SE | | | | |
| ES 2270868 | T3 | 20070416 | ES 2000-959232 | 20000814 |
| IN 2002DN00160 | A | 20061229 | IN 2002-DN160 | 20020207 |

| | | | | |
|------------------------|----|----------|-----------------|-------------|
| MX 2002PA01449 | A | 20020702 | MX 2002-PA1449 | 20020211 |
| ZA 2002001158 | A | 20030512 | ZA 2002-1158 | 20020211 |
| NO 2002000725 | A | 20020408 | NO 2002-725 | 20020213 |
| NO 324044 | B1 | 20070730 | | |
| BG 106510 | A | 20021031 | BG 2002-106510 | 20020311 |
| HK 1051500 | A1 | 20070202 | HK 2003-103786 | 20030527 |
| US 2004132809 | A1 | 20040708 | US 2003-677756 | 20031003 |
| US 7034043 | B2 | 20060425 | | |
| US 2006166961 | A1 | 20060727 | US 2006-362043 | 20060227 |
| PRIORITY APPLN. INFO.: | | | | |
| | | | US 1999-148845P | P 19990813 |
| | | | EP 2000-959232 | A3 20000814 |
| | | | US 2000-638652 | A1 20000814 |
| | | | WO 2000-US22285 | W 20000814 |
| | | | US 2003-677756 | A1 20031003 |

OTHER SOURCE(S): MARPAT 134:193741

AB Cell adhesion inhibitors of the general formula R3-L-L'-R1 (R1 = H, C1-10alkyl, C2-10alkenyl or -alkynyl, cycloalkyl, cycloalkylalkyl, -alkenyl, or -alkynyl; L' and L are hydrocarbon linker moieties having 1-5 or 1-14 carbons, resp., which are optionally substituted and interrupted by, or terminally attached to, various groups; R3 = alkyl, cycloalkyl, aryl, aralkyl, aryloxy, arylamino, heterocyclyl, etc.) were prepared. An inhibitor of the present invention interacts with VLA-4 mols. to inhibit VLA-4 dependent cell adhesion. Thus, N2-[N-[(3,5-dichlorophenyl)sulfonyl]-L-prolyl]-N4-[N-(o-MePUPA)-N-methyl-L-leucyl]-L-2,4-diaminobutyric acid [o-MePUPA = [4-[[[(2-methylphenyl)amino]carbonyl]amino]phenyl]acetyl] was prepared via peptide coupling reactions in solution

IT 327612-71-5P 327612-72-6P 327612-73-7P

327613-58-1P

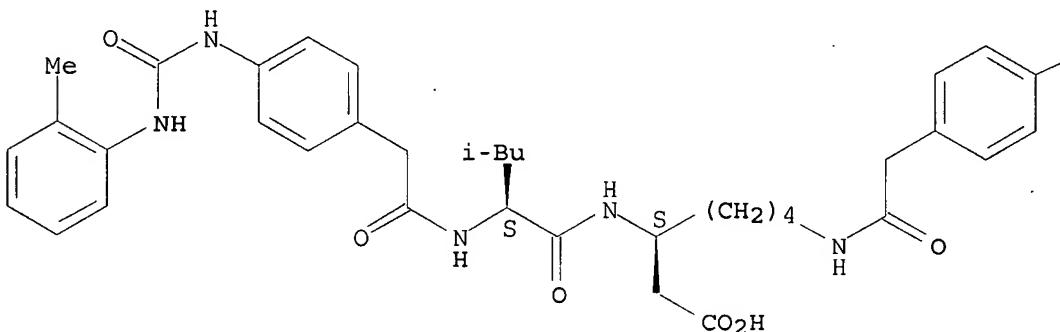
RL: SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of peptide derivs. as cell adhesion inhibitors)

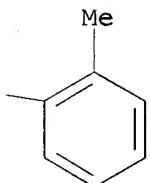
RN 327612-71-5 CAPLUS

CN Heptanoic acid, 3-[[[(2S)-4-methyl-2-[[[4-[[[(2-methylphenyl)amino]carbonyl]amino]phenyl]acetyl]amino]-1-oxopentyl]amino]-7-[[[4-[[[(2-methylphenyl)amino]carbonyl]amino]phenyl]acetyl]amino]-, (3S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A

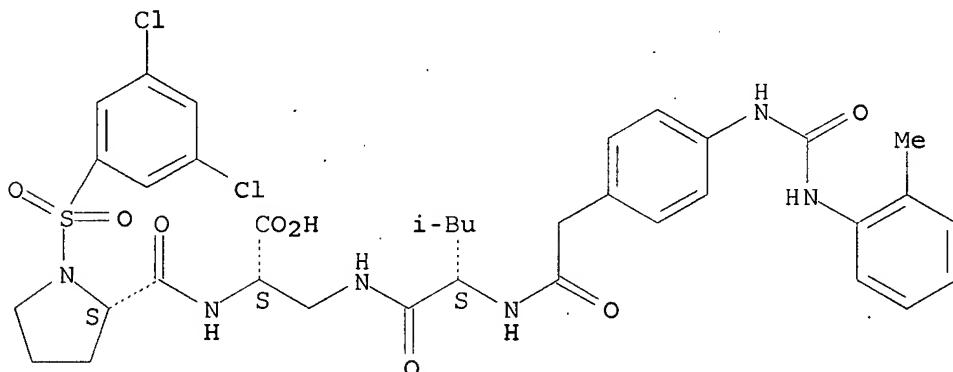




RN 327613-58-1 CAPLUS

CN L-Alanine, 1-[(3,5-dichlorophenyl)sulfonyl]-L-prolyl-3-[(2S)-4-methyl-2-[[4-[[[(2-methylphenyl)amino]carbonyl]amino]phenyl]acetyl]amino]-1-oxopentyl]amino] - (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 18 OF 26 CAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 2000:353355 CAPLUS

DOCUMENT NUMBER: 132:342664

TITLE: Bio-1211 (Biogen)

AUTHOR(S): Bolger, Gordon T.

CORPORATE SOURCE: Bio-Mega/Boehringer Ingelheim Research Inc, Lavel, QC, H7S 2G5, Can.

SOURCE: Current Opinion in Anti-Inflammatory and Immunomodulatory Investigational Drugs (2000), 2(2), 108-112

CODEN: COAIFI; ISSN: 1464-8474

PUBLISHER: PharmaPress Ltd.

DOCUMENT TYPE: Journal; General Review

LANGUAGE: English

AB A review with 45 refs. Biogen, in collaboration with Merck & Co, was developing late activator VLA4 ($\alpha 4\beta 1$) integrin antagonists for the potential treatment of inflammatory conditions. Merck carried out a phase IIa trial with the lead compound, BIO-1211, for asthma, but has recently discontinued development due to a lack of efficacy. Biogen is also no longer carrying out clin. studies with BIO-1211 and it is unclear at this time if the drug is still being investigated for any of the other reported indications, although a recent patent application, WO-09961421, suggests that Biogen may still be investigating the potential of this class of drug in inflammatory or immune disorders. Under the collaborative agreement, each company had worldwide rights to certain

indications; Merck had rights for asthma and Biogen retained the rights to a number of smaller indications including multiple sclerosis, inflammatory bowel disease, renal indications and most diseases in which the US patient population is less than 200,000. VLA4 inhibitors show anti-inflammatory action by inhibition of binding between adhesion factors and leukocytes, but with no loss of basophil function, and they have the advantage of specificity not seen with existing drugs. In Feb. 1999, for the asthma indication (Merck), Lehman Brothers had predicted 40% probabilities that the compound would reach the US and ex-US markets, and launch onto these markets by 2003. Peak annual sales of US \$500 million (US) and US \$500 million (outside US) were predicted on this basis, both in 2010.

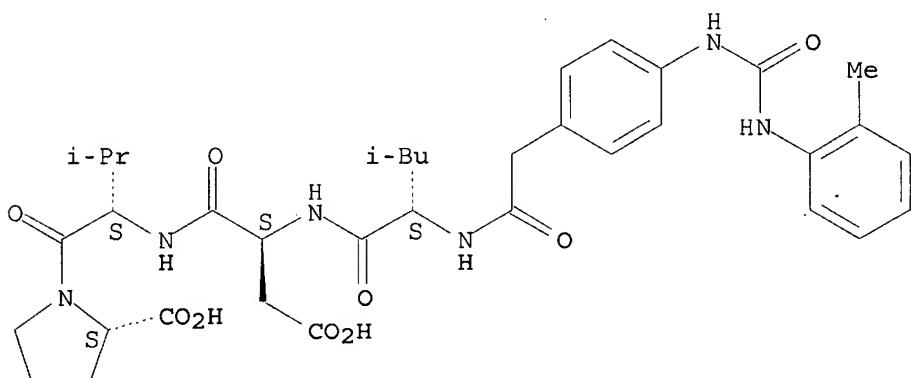
IT 187735-94-0, Bio-1211

RL: ADV (Adverse effect, including toxicity); BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(status of development of anti-inflammatory bio-1211)

RN 187735-94-0 CAPLUS

CN L-Proline, N-[2-[4-[[[(2-methylphenyl)amino]carbonyl]amino]phenyl]acetyl]-L-leucyl-L- α -aspartyl-L-valyl- (CA INDEX NAME)

Absolute stereochemistry.



L7 ANSWER 19 OF 26 CAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER:

2000:312195 CAPLUS

DOCUMENT NUMBER:

133:26389

TITLE:

BIO-1211 Biogen

AUTHOR(S):

Bolger, Gordon T.

CORPORATE SOURCE:

Bio-Mega/Boehringer Ingelheim Research Inc, Lavel, QC, H7S 2G5, Can.

SOURCE:

IDrugs (2000); 3(5), 536-540

CODEN: IDRUFN; ISSN: 1369-7056

PUBLISHER:

Current Drugs Ltd.

DOCUMENT TYPE:

Journal; General Review

LANGUAGE:

English

AB A review with many refs. is given. Biogen, in collaboration with Merck & Co, is developing late activator VLA-4 ($\alpha 4\beta 1$) integrin antagonists for the potential treatment of inflammatory conditions. Merck has begun phase II trials with the lead compound, BIO-1211, for asthma. Biogen is still conducting preclin. research for its designated indications. Under the collaborative agreement, each company has worldwide rights to certain indications; Merck has rights for asthma and Biogen retains the rights to a number of smaller indications, including multiple sclerosis, inflammatory bowel disease, renal indications and most diseases in which the US patient population is <200,000. VLA-4 inhibitors show anti-inflammatory action by inhibition of binding between adhesion factors and leukocytes, but with no loss of basophil function, and they

have the advantage of specificity not seen with existing drugs. In Feb. 1999, Lehman Brothers predicted 40% probabilities that the compound would reach the US and ex-US markets for the asthma indication (Merck), and launch onto these markets by 2003. Peak annual sales of US \$500 million (US) and US \$500 million (outside US) are predicted, both in 2010.

IT 187735-94-0, BIO-1211

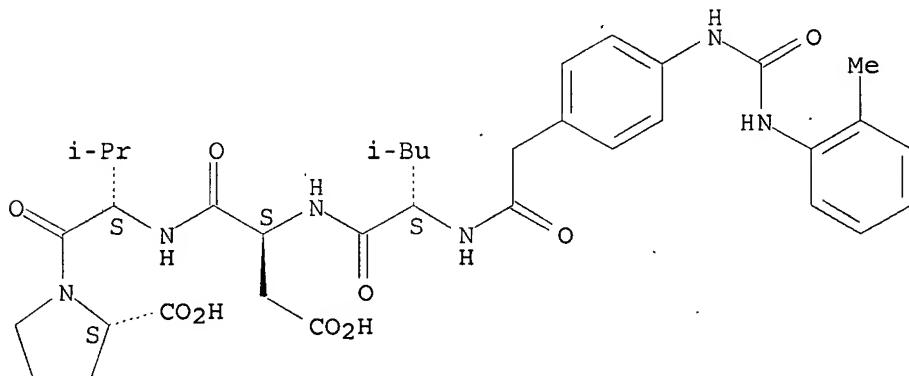
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(BIO-1211, an antiinflammatory agent)

RN 187735-94-0 CAPLUS

CN L-Proline, N-[2-[4-[[[(2-methylphenyl)amino]carbonyl]amino]phenyl]acetyl]-L-leucyl-L- α -aspartyl-L-valyl- (CA INDEX NAME)

Absolute stereochemistry.



L7 ANSWER 20 OF 26 CAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 1999:317616 CAPLUS

DOCUMENT NUMBER: 131:126890

TITLE: Multiple activation states of integrin $\alpha 4\beta 1$ detected through their different affinities for a small molecule ligand

AUTHOR(S): Chen, Ling Ling; Whitty, Adrian; Lobb, Roy R.; Adams, Steven P.; Pepinsky, R. Blake

CORPORATE SOURCE: Biogen, Inc., Cambridge, MA, 02142, USA

SOURCE: Journal of Biological Chemistry (1999), 274(19), 13167-13175

CODEN: JBCHA3; ISSN: 0021-9258

PUBLISHER: American Society for Biochemistry and Molecular Biology

DOCUMENT TYPE: Journal

LANGUAGE: English

AB We have used the highly specific $\alpha 4\beta 1$ inhibitor 4-((N'-2-methylphenyl)ureido)-phenylacetyl-leucine-aspartic acid-valine-proline (BIO1211) as a model LDV-containing ligand to study $\alpha 4\beta 1$ integrin-ligand interactions on Jurkat cells under diverse conditions that affect the activation state of $\alpha 4\beta 1$. Observed KD values for BIO1211 binding ranged from a value of 20-40 nM in the nonactivated state of the integrin that exists in 1 mM Mg²⁺, 1 mM Ca²⁺ to 100 pM in the activated state seen in 2 mM Mn²⁺ to 18 pM when binding was measured after coactivation by 2 mM Mn²⁺ plus 10 μ g/mL of the integrin-activating monoclonal antibody TS2/16. The large range in KD values was governed almost exclusively by differences in the dissociation rates of the integrin-BIO1211 complex, which ranged from 0.17×10^{-4} s⁻¹ to $>140 \times 10^{-4}$ s⁻¹. Association rate consts. varied only slightly under the same conditions, all falling in the narrow range from 0.9 to 2.7×10^6 M⁻¹

s-1. The further increase in affinity observed upon co-activation by divalent cations and TS2/16 compared with that observed at saturating concns. of

metal ions or TS2/16 alone indicates that the mechanism by which these factors bring about activation are distinct and identified a previously unrecognized high affinity state on $\alpha 4\beta 1$, that had not been detected by conventional assay methods. Similar changes in affinity were observed when the binding properties of vascular cell adhesion mol.-1 and CS1 to $\alpha 4\beta 1$ were studied, indicating that the different affinity states detected with BIO1211 are an inherent property of the integrin.

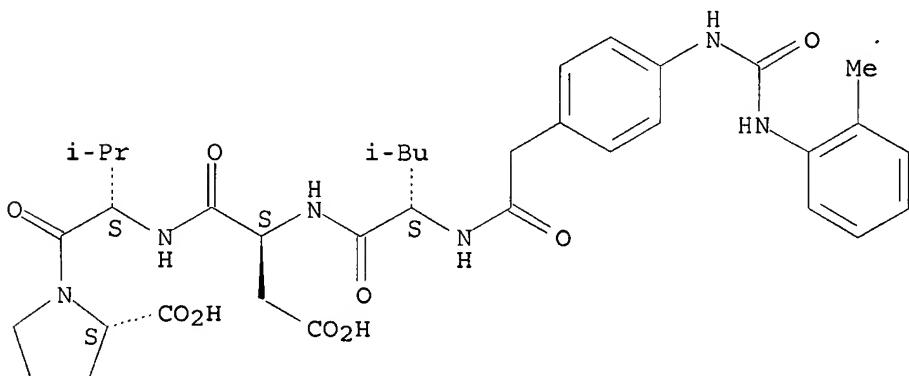
IT 187735-94-0

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(multiple activation states of integrin $\alpha 4\beta 1$ detected through different affinities for small mol. ligand)

RN 187735-94-0 CAPLUS

CN L-Proline, N-[2-[4-[[[(2-methylphenyl)amino]carbonyl]amino]phenyl]acetyl]-L-leucyl-L- α -aspartyl-L-valyl- (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT:

44 THERE ARE 44 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 21 OF 26 CAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 1999:161426 CAPLUS

DOCUMENT NUMBER: 130:332268

TITLE: Selective, Tight-Binding Inhibitors of Integrin $\alpha 4\beta 1$ That Inhibit Allergic Airway Responses

AUTHOR(S): Lin, Ko-chung; Ateeq, Humayun S.; Hsiung, Sherry H.; Chong, Lillian T.; Zimmerman, Craig N.; Castro, Alfredo; Lee, Wen-cherng; Hammond, Charles E.; Kalkunte, Sandhya; Chen, Ling-Ling; Pepinsky, R. Blake; Leone, Diane R.; Sprague, Andrew G.; Abraham, William M.; Gill, Alan; Lobb, Roy R.; Adams, Steven P.

CORPORATE SOURCE: Biogen Inc., Cambridge, MA, 02142, USA

SOURCE: Journal of Medicinal Chemistry (1999), 42(5), 920-934

CODEN: JMCMAR; ISSN: 0022-2623

PUBLISHER: American Chemical Society

DOCUMENT TYPE: Journal

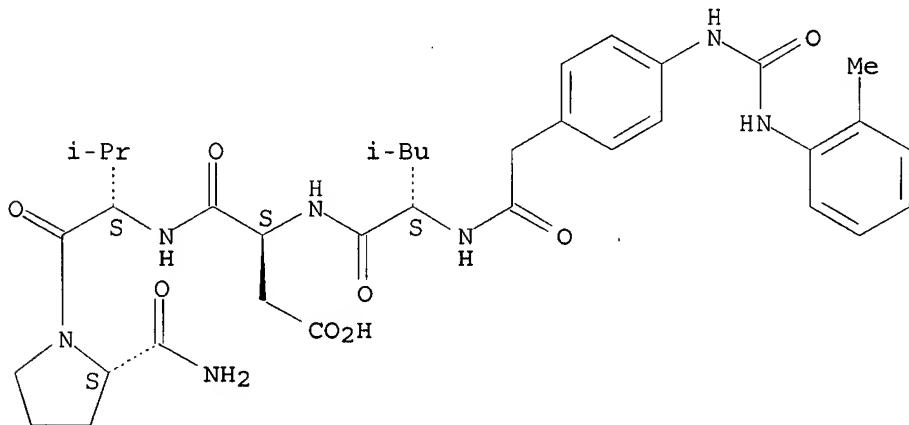
LANGUAGE: English

AB Integrin $\alpha 4\beta 1$ mediates leukocyte recruitment, activation, mediator release, and apoptosis inhibition, and it plays a central role in inflammatory pathophysiol. High-affinity, selective inhibitors of $\alpha 4\beta 1$, based on the Leu-Asp-Val (LDV) sequence from the alternatively spliced connecting segment-1 (CS-1) peptide of cellular fibronectin, are described that employ a novel N-terminal peptide "cap"

strategy. One inhibitor, BIO-1211, was apprx.106-fold more potent than the starting peptide and exhibited tight-binding properties ($k_{off} = 1.4 \pm 10^{-4} \text{ s}^{-1}$, $K_D = 70 \text{ pM}$), a remarkable finding for a noncovalent, small-mol. inhibitor of a protein receptor. BIO-1211 was also 200-fold selective for the activated form of $\alpha 4\beta 1$, and it stimulated expression of ligand-induced epitopes on the integrin $\beta 1$ subunit, a property consistent with occupancy of the receptor's ligand-binding site. Pretreatment of allergic sheep with a 3-mg nebulized dose of BIO-1211 inhibited early and late airway responses following antigen challenge and prevented development of nonspecific airway hyperresponsiveness to carbachol. These results show that highly selective and potent small-mol. antagonists can be identified to integrins with primary specificity for peptide domains other than Arg-Gly-Asp (RGD); they confirm the generality of integrins as small mol. targets; and they validate $\alpha 4\beta 1$ as a therapeutic target for asthma.

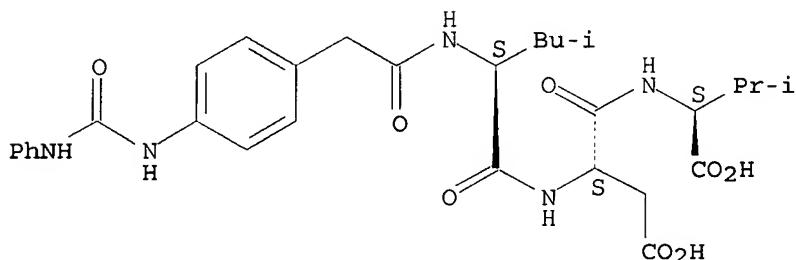
IT 187735-36-0 187735-91-7 187735-94-0
 187737-31-1 187737-40-2 224577-01-9
 RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
 (synthesis of integrin $\alpha 4\beta 1$ inhibitors that inhibit allergic airway responses)
 RN 187735-36-0 CAPLUS
 CN L-Prolinamide, N-[[4-[[[(2-methylphenyl)amino]carbonyl]amino]phenyl]acetyl]-L-leucyl-L- α -aspartyl-L-valyl- (9CI) (CA INDEX NAME)

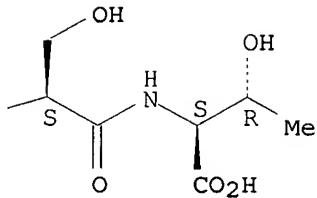
Absolute stereochemistry.



RN 187735-91-7 CAPLUS
 CN L-Valine, N-[[4-[[[(phenylamino)carbonyl]amino]phenyl]acetyl]-L-leucyl-L- α -aspartyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

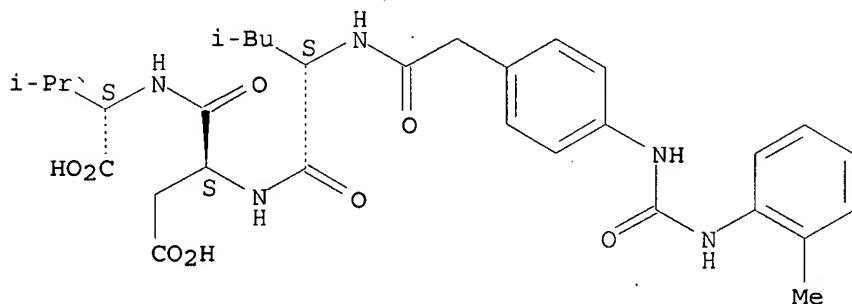




RN 187737-40-2 CAPLUS

CN L-Valine, N-[2-[4-[[[(2-methylphenyl)amino]carbonyl]amino]phenyl]acetyl]-L-leucyl-L- α -aspartyl- (CA INDEX NAME)

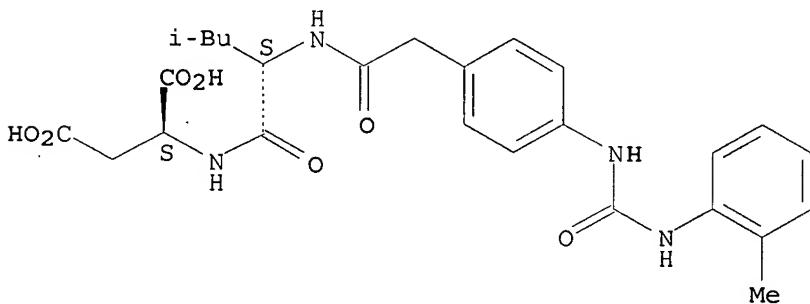
Absolute stereochemistry.



RN 224577-01-9 CAPLUS

CN L-Aspartic acid, N-[[4-[[[(2-methylphenyl)amino]carbonyl]amino]phenyl]acet yl]-L-leucyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT:

39

THERE ARE 39 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 22 OF 26 CAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 1998:677800 CAPLUS

DOCUMENT NUMBER: 129:276355

TITLE: Preparation of peptides and peptidomimetics as VLA-4 antagonists

INVENTOR(S): He, Ya-Bo; Elices, Mariano J.; Arrhenius, Thomas S.

PATENT ASSIGNEE(S): Cytel Corporation, USA

SOURCE: PCT Int. Appl., 153 pp.

CODEN: PIXXD2

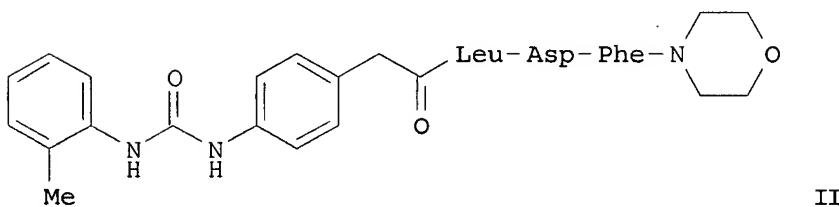
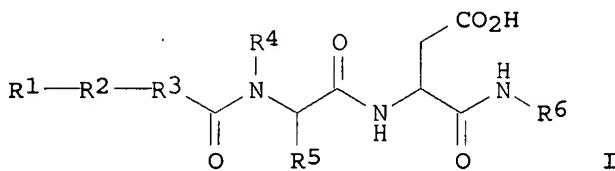
DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|--|------|-------------------|-----------------|------------|
| WO 9842656 | A1 | 19981001 | WO 1998-US5709 | 19980320 |
| W: CA, JP | | | | |
| RW: AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE | | | | |
| PRIORITY APPLN. INFO.: | | | US 1997-821825 | A 19970321 |
| OTHER SOURCE(S): | | MARPAT 129:276355 | | |
| GI | | | | |



AB Title compds. I [R1 = alkyl, adamantyl, (un)substituted non-heterocyclic, heterocyclic, aromatic, or partially or fully saturated ring; R2 = lower alkyl, alkenyl, or alkynyl group in which each group optionally can contain a carbonyl, ether, thioether, aminocarbonyl group, etc., or E-C(R7)-F where R7 = S, O; E = CX1X2, NX3, or O; F = CX4X5, NX6, or O; X1-X6 = independently H or a lower alkyl, with the proviso that E and F are not simultaneously oxygen atoms and if R1 is an alkyl group, R2 must be of formula E-C(R7)-F; R3 = 5-, 6-, 6,5-, or 6,6- membered aromatic ring optionally containing 1-3 heteroatoms selected from the group O, N, S; R4 = H, lower alkyl; R5 = H, lower alkyl, (un)substituted lower alkyl amido group, or a 5- or 6- membered non-heterocyclic saturated ring connected directly by a bond or through a lower alkyl group; R6 = substituted azepine, or CH(R8)COAR9R10 where A = N, O; R8 = H, lower alkyl, hydroxyalkyl, thioalkyl, a ring structure connected directly by a bond or through a lower alkyl group, or R8 and R9 together form a ring structure, etc.; R9 = lower alkyl, hydroxyalkyl, morpholino group, or together with R10 form a ring structure; R10 = (un)substituted lower alkyl, or together with R9 form a ring structure; when A = O, R10 is absent] and pharmaceutically-acceptable derivs. thereof. were prepared as VLA-4 antagonists. Thus, II (solution phase preparation given) was assayed for binding inhibition potency (IC50 = 0.4 nM) toward Jurkat cells.

IT 213989-63-0P

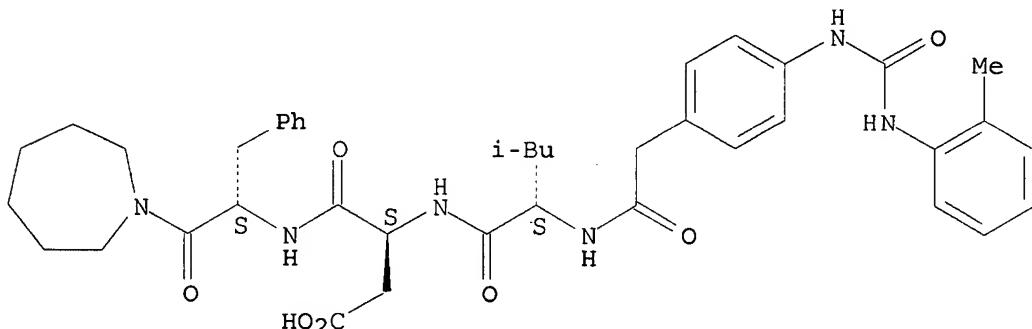
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)

(preparation of peptides and peptidomimetics as VLA-4 antagonists)

RN 213989-63-0 CAPLUS

CN L- α -Asparagine, N-[(4-[[[(2-methylphenyl)amino]carbonyl]amino]phenyl]acetyl]-L-leucyl-N-[(1S)-2-(hexahydro-1H-azepin-1-yl)-2-oxo-1-(phenylmethyl)ethyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



IT 213989-21-0P 213989-23-2P 213989-27-6P

213989-29-8P 213989-35-6P 213989-39-0P

213989-40-3P 213989-41-4P 213989-42-5P

213989-46-9P 213989-48-1P 213989-53-8P

213989-55-0P 213989-56-1P 213989-58-3P

213989-61-8P 213989-64-1P 213989-66-3P

213989-68-5P 213989-70-9P 213989-72-1P

213989-75-4P 213989-77-6P 213989-87-8P

213989-88-9P 213990-01-3P 213990-08-0P

213990-09-1P

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

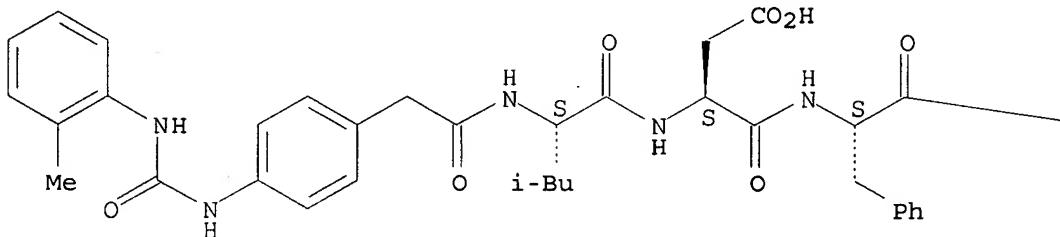
(preparation of peptides and peptidomimetics as VLA-4 antagonists)

RN 213989-21-0 CAPLUS

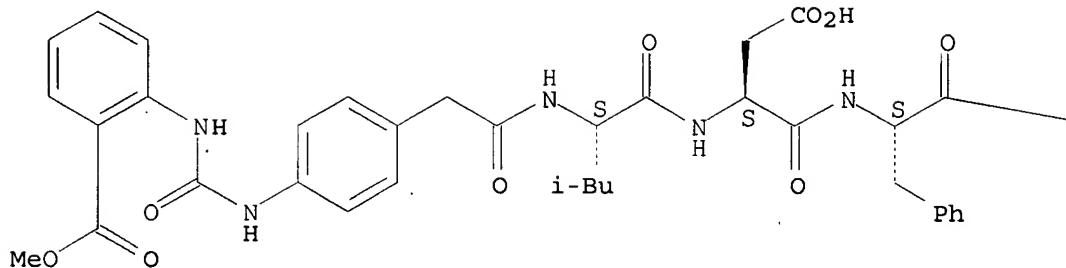
CN L- α -Asparagine, N-[(4-[[[(2-methylphenyl)amino]carbonyl]amino]phenyl]acetyl]-L-leucyl-N-[(1S)-2-(4-morpholinyl)-2-oxo-1-(phenylmethyl)ethyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry:

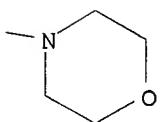
PAGE 1-A



PAGE 1-A



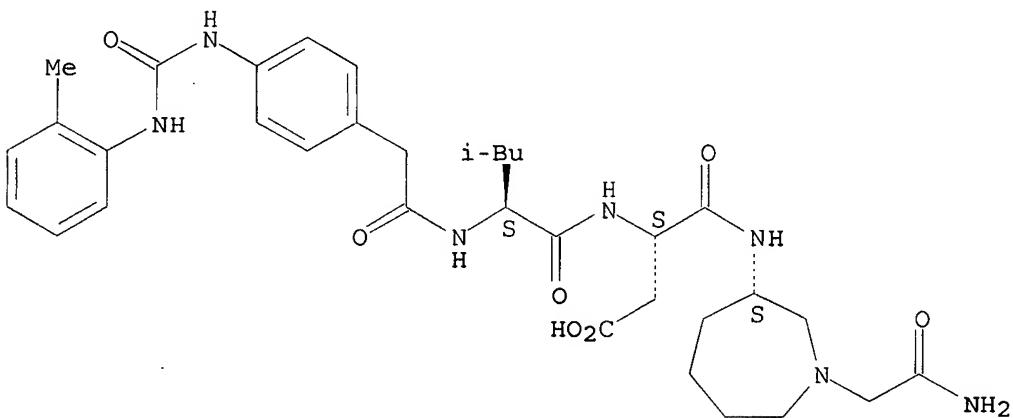
PAGE 1-B



RN 213990-09-1 CAPLUS

CN L- α -Asparagine, N-[[4-[[[(2-methylphenyl)amino]carbonyl]amino]phenyl]acetyl]-L-leucyl-N-[(3S)-1-(2-amino-2-oxoethyl)hexahydro-1H-azepin-3-yl]-(9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT:

5

THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 23 OF 26 CAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 1998:106085 CAPLUS

DOCUMENT NUMBER: 128:176149

TITLE: Molecular model for VLA-4 inhibitors, and inhibitor identification

INVENTOR(S): Singh, Juswinder; Zheng, Zhongli; Sprague, Peter; Van Vlijmen, Herman W. T.; Castro, Alfredo C.; Adams, Steven P.

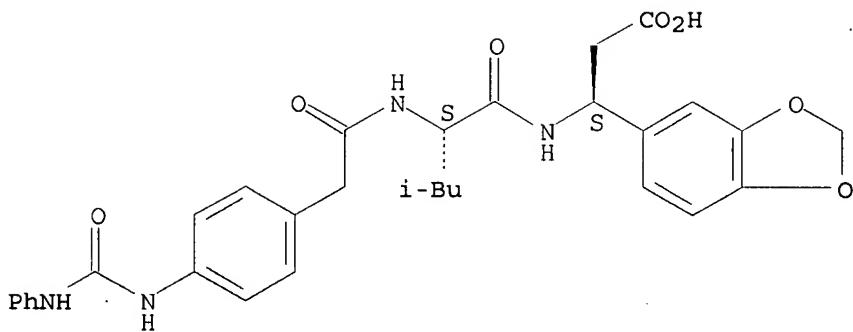
PATENT ASSIGNEE(S): Biogen, Inc., USA; Singh, Juswinder; Zheng, Zhongli; Sprague, Peter; Van Vlijmen, Herman W. T.; Castro,

SOURCE: Alfredo C.; Adams, Steven P.
 PCT Int. Appl., 82 pp.
 CODEN: PIXXD2
 DOCUMENT TYPE: Patent
 LANGUAGE: English
 FAMILY ACC. NUM. COUNT: 2
 PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|------|----------|--------------------|-------------|
| WO 9804913 | A1 | 19980205 | WO 1997-US13008 | 19970724 |
| W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW | | | | |
| RW: GH, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG | | | | |
| CA 2261974 | A1 | 19980205 | CA 1997-2261974 | 19970724 |
| AU 9737385 | A | 19980220 | AU 1997-37385 | 19970724 |
| EP 914605 | A1 | 19990512 | EP 1997-934288 | 19970724 |
| EP 914605 | B1 | 20070530 | | |
| R: AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LI, LU, MC, NL, PT, SE, LT, LV, RO, SI | | | | |
| CN 1230110 | A | 19990929 | CN 1997-197953 | 19970724 |
| HU 9903142 | A2 | 20000128 | HU 1999-3142 | 19970724 |
| HU 9903142 | A3 | 20000628 | | |
| CN 1478472 | A | 20040303 | CN 2003-2003146679 | 19970724 |
| SG 124234 | A1 | 20060830 | SG 2001-382 | 19970724 |
| AT 339196 | T | 20061015 | AT 1997-934289 | 19970724 |
| ES 2271971 | T3 | 20070416 | ES 1997-934289 | 19970724 |
| CZ 298080 | B6 | 20070613 | CZ 1999-232 | 19970724 |
| AT 363658 | T | 20070615 | AT 1997-934288 | 19970724 |
| CZ 298089 | B6 | 20070620 | CZ 2003-1362 | 19970724 |
| ES 2285735 | T3 | 20071116 | ES 1997-934288 | 19970724 |
| KR 2000029538 | A | 20000525 | KR 1999-700595 | 19990125 |
| US 6552216 | B1 | 20030422 | US 1999-236784 | 19990125 |
| BG 64470 | B1 | 20050430 | BG 1999-103193 | 19990222 |
| BG 108806 | A | 20050430 | BG 1999-108806 | 19990222 |
| BG 64902 | B1 | 20060831 | | |
| AU 759063 | B2 | 20030403 | AU 2001-91330 | 20011114 |
| PRIORITY APPLN. INFO.: | | | US 1996-22890P | P 19960725 |
| | | | US 1996-32786P | P 19961206 |
| | | | US 1997-57002P | P 19970630 |
| | | | AU 1997-37386 | A3 19970724 |
| | | | WO 1997-US13008 | W 19970724 |

OTHER SOURCE(S): MARPAT 128:176149
 AB Pharmacophore models of VLA-4 inhibitors are disclosed, as are methods of identifying novel inhibitors and novel inhibitors identified by these methods.
 IT 181520-66-1 181523-34-2 187735-94-0
 RL: PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
 (mol. model for VLA-4 inhibitors, and inhibitor identification)
 RN 181520-66-1 CAPLUS
 CN 1,3-Benzodioxole-5-propanoic acid, β -[[[(2S)-4-methyl-1-oxo-2-[[[4-[(phenylamino)carbonyl]amino]phenyl]acetyl]amino]pentyl]amino]-, (BS)- (9CI) (CA INDEX NAME)

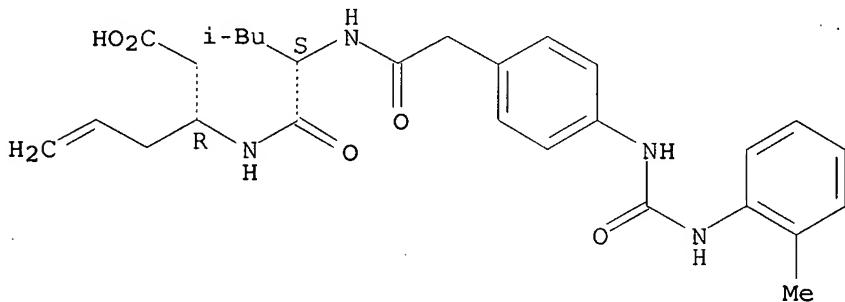
Absolute stereochemistry.



RN 181523-34-2 CAPLUS

CN 5-Hexenoic acid, 3-[(2S)-4-methyl-2-[[[4-[[[(2-methylphenyl)amino]carbonyl]amino]phenyl]acetyl]amino]-1-oxopentyl]amino]-, (3R)- (9CI) (CA INDEX NAME)

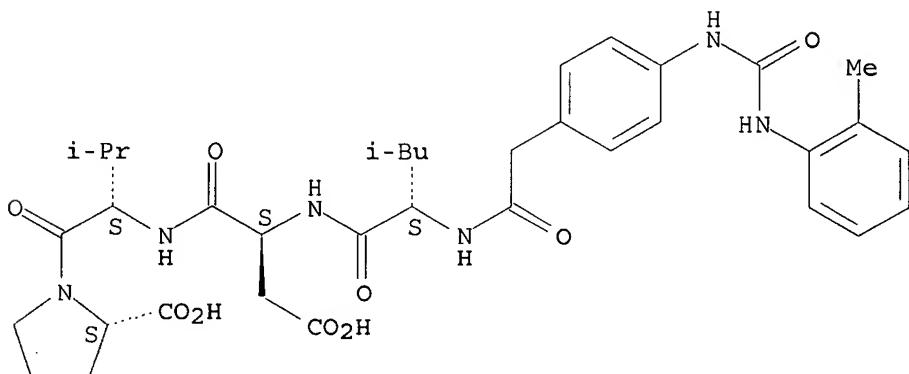
Absolute stereochemistry.



RN 187735-94-0 CAPLUS

CN L-Proline, N-[2-[4-[[[[(2-methylphenyl)amino]carbonyl]amino]phenyl]acetyl]-L-leucyl-L- α -aspartyl-L-valyl- (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT:

1

THERE ARE 1 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 24 OF 26 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1997:395127 CAPLUS
DOCUMENT NUMBER: 127:103716

TITLE: Potent antagonists of the leukocyte integrin alpha-4 beta-1 (VLA-4)
 AUTHOR(S): Adams, Steve
 CORPORATE SOURCE: Biogen, USA
 SOURCE: Drug Discovery Technology: Interdisciplinary Approaches to Accelerate Drug Development, [IBC Conference, "Drug Discovery Technology: Interdisciplinary Approaches to Accelerate Drug Development"], Boston, Aug. 19-22, 1996 (1997), Meeting Date 1996, 5.2.1-5.2.18. Editor(s): Hori, Wendy. International Business Communications: Southborough, Mass.
 CODEN: 64OVAX

DOCUMENT TYPE: Conference; General Review

LANGUAGE: English

AB A review with no cited refs. The role of leukocyte α -4 β -1 integrin (VLA-4) in the pathogenicity of inflammatory diseases are discussed. Using a classical peptide mimetic approach, very potent sub-nanomolar inhibitors of VLA-4 have been developed. Candidate VLA-4 inhibitors (e.g., BIO-1211) are highly selective, and some are equipotent against α -4 β -7. The different classes of compds. that have been identified are exquisitely potent in the DTH model and are also very potent in a pathophysiol. model of airway hyper-responsiveness. BIO-1211 is currently in late stage of preclin. development.

IT 187735-94-0, BIO 1211

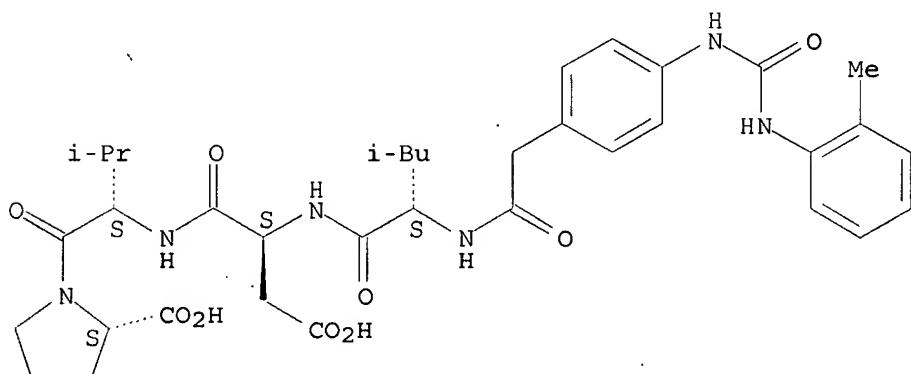
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(potent antagonists of the leukocyte α 4 β 1-integrin (VLA-4))

RN 187735-94-0 CAPLUS

CN L-Proline, N-[2-[4-[[[(2-methylphenyl)amino]carbonyl]amino]phenyl]acetyl]-L-leucyl-L- α -aspartyl-L-valyl- (CA INDEX NAME)

Absolute stereochemistry.



L7 ANSWER 25 OF 26 CAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 1997:207658 CAPLUS

DOCUMENT NUMBER: 126:199840

TITLE: Preparation of peptide derivatives as cell adhesion inhibitors

INVENTOR(S): Lin, Ko-Chung; Adams, Steven P.; Castro, Alfredo C.; Zimmerman, Craig N.; Cuervo, Julio Hernan; Lee, Wen-Cherng; Hammond, Charles E.; Carter, Mary Beth; Almquist, Ronald G.; Ensinger, Carol Lee

PATENT ASSIGNEE(S): Biogen, Inc., USA; Lin, Ko-Chung; Adams, Steven, P.; Castro, Alfredo, C.; Zimmerman, Craig, N.; Cuervo,

Julio, Hernan; Lee, Wen-Cherng; Hammond, Charles, E.;
Carter, Mary, Beth; et al.

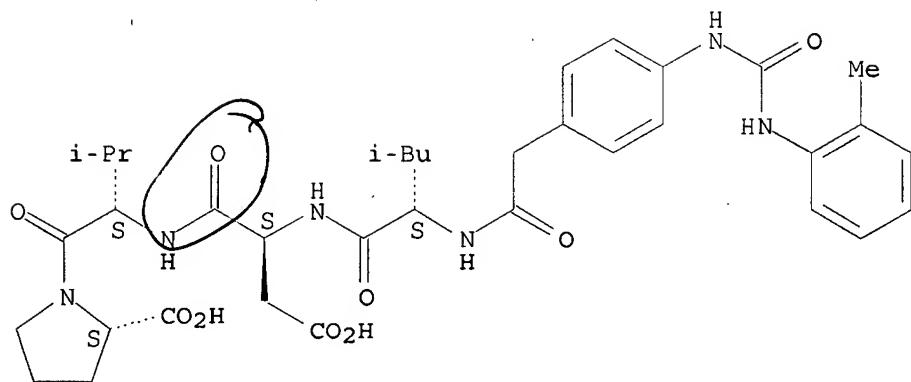
SOURCE: PCT Int. Appl., 117 pp.
CODEN: PIXXD2

DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|------|----------|------------------|-------------|
| WO 9703094 | A1 | 19970130 | WO 1996-US11570 | 19960711 |
| W: AL, AM, AT, AU, AZ, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG | | | | |
| RW: KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA | | | | |
| US 6248713 | B1 | 20010619 | US 1995-498237 | 19950711 |
| CA 2226868 | A1 | 19970130 | CA 1996-2226868 | 19960711 |
| AU 9664894 | A | 19970210 | AU 1996-64894 | 19960711 |
| AU 716276 | B2 | 20000224 | | |
| EP 842196 | A1 | 19980520 | EP 1996-924444 | 19960711 |
| EP 842196 | B1 | 20071121 | | |
| R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI | | | | |
| CN 1193325 | A | 19980916 | CN 1996-196380 | 19960711 |
| HU 9802202 | A2 | 19990128 | HU 1998-2202 | 19960711 |
| BR 9609782 | A | 19990309 | BR 1996-9782 | 19960711 |
| JP 11511124 | T | 19990928 | JP 1996-505989 | 19960711 |
| NZ 312950 | A | 20000128 | NZ 1996-312950 | 19960711 |
| EE 3694 | B1 | 20020415 | EE 1997-362 | 19960711 |
| EE 200200384 | A | 20021015 | EE 2002-384 | 19960711 |
| PL 188446 | B1 | 20050228 | PL 1996-324491 | 19960711 |
| IL 122783 | A | 20050831 | IL 1996-122783 | 19960711 |
| RO 121032 | B1 | 20061130 | RO 1998-33 | 19960711 |
| TW 570927 | B | 20040111 | TW 1996-85108493 | 19960712 |
| FI 9800033 | A | 19980305 | FI 1998-33 | 19980109 |
| NO 9800097 | A | 19980311 | NO 1998-97 | 19980109 |
| BG 63876 | B1 | 20030430 | BG 1998-102241 | 19980210 |
| US 6239108 | B1 | 20010529 | US 1998-983391 | 19980810 |
| US 6596687 | B1 | 20030722 | US 2000-482296 | 200000113 |
| AU 758886 | B2 | 20030403 | AU 2000-36445 | 200000525 |
| US 6875743 | B1 | 20050405 | US 2000-724139 | 200001128 |
| PRIORITY APPLN. INFO.: | | | US 1995-498237 | A 19950711 |
| | | | AU 1996-64894 | A3 19960711 |
| | | | WO 1996-US11570 | W 19960711 |
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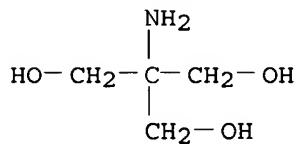
OTHER SOURCE(S): MARPAT 126:199840

AB The present invention relates to novel peptide derivs. that are useful for inhibition and prevention of cell adhesion and cell adhesion-mediated pathologies. This invention also relates to pharmaceutical formulations comprising these compds. and methods of using them for inhibition and prevention of cell adhesion and cell adhesion-mediated pathologies. The compds. and pharmaceutical composition of this invention can be used as therapeutic or prophylactic agents. They are particularly well-suited for treatment of many inflammatory and autoimmune diseases. Thus, coupling of 4-(2-MeC6H4NHCONH)C6H4CH2CO2H (preparation given) with protected peptide H-Leu-Asp(OCH2Ph)-Val-OCH2Ph (preparation given), followed by catalytic hydrogenolysis, gave cell adhesion inhibitor peptide 4-(2-MeC6H4NHCONH)C6H4CH2CO-Leu-Asp-Val-OH (I). All 408 prepared peptide derivs., including I, inhibited VLA4-dependent adhesion to a bovine serum albumin conjugate with H-Cys-Tyr-Asp-Glu-Leu-Pro-Gln-Leu-Val-Thr-Leu-Pro-



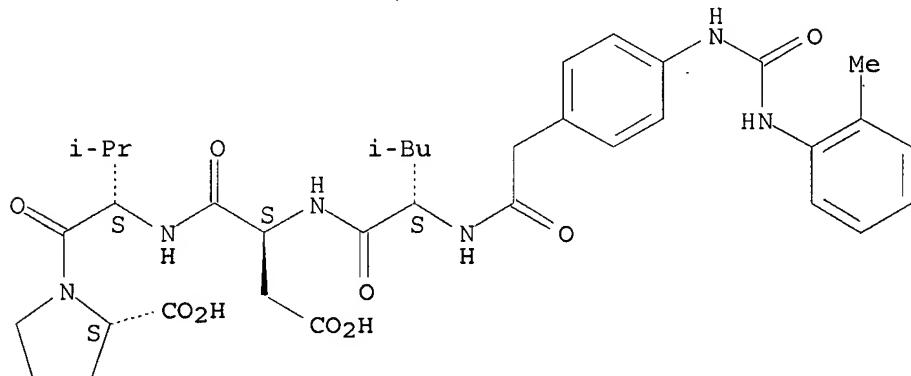
CM 2

CRN 77-86-1
 CMF C4 H11 N O3



RN 187737-53-7 CAPLUS
 CN L-Proline, N-[[4-[[[(2-methylphenyl)amino]carbonyl]amino]phenyl]acetyl]-L-leucyl-L- α -aspartyl-L-valyl-, disodium salt (9CI) (CA INDEX NAME)

Absolute stereochemistry.



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L7 ANSWER 26 OF 26 CAPLUS COPYRIGHT 2007 ACS on STN
 ACCESSION NUMBER: 1996:593835 CAPLUS
 DOCUMENT NUMBER: 125:248489
 TITLE: Preparation of dipeptide derivatives as cell adhesion inhibitors

INVENTOR(S): Adams, Steven P.; Lin, Ko-Chung; Lee, Wen-Cherng; Castro, Alfredo C.; Zimmerman, Craig N.; Hammond, Charles E.; Liao, Yu-Sheng; Cuervo, Julio Hernan; Singh, Juswinder

PATENT ASSIGNEE(S): Biogen, Inc., USA

SOURCE: PCT Int. Appl., 169 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 2

PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|------|----------|------------------|-------------|
| WO 9622966 | A1 | 19960801 | WO 1996-US1349 | 19960118 |
| W: AL, AM, AT, AU, AZ, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI | | | | |
| RW: KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE | | | | |
| US 6306840 | B1 | 20011023 | US 1995-376372 | 19950123 |
| CA 2211181 | A1 | 19960801 | CA 1996-2211181 | 19960118 |
| AU 9649115 | A | 19960814 | AU 1996-49115 | 19960118 |
| AU 718926 | 'B2 | 20000504 | | |
| EP 805796 | A1 | 19971112 | EP 1996-905316 | 19960118 |
| EP 805796 | B1 | 20021211 | | |
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| BR 9606778 | A | 19980106 | BR 1996-6778 | 19960118 |
| CN 1177343 | A | 19980325 | CN 1996-192270 | 19960118 |
| HU 9702461 | A2 | 19980428 | HU 1997-2461 | 19960118 |
| HU 223350 | B1 | 20040628 | | |
| JP 10513160 | T | 19981215 | JP 1996-523071 | 19960118 |
| EP 1142867 | A2 | 20011010 | EP 2001-107877 | 19960118 |
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| AT 229498 | T | 20021215 | AT 1996-905316 | 19960118 |
| ES 2183937 | T3 | 20030401 | ES 1996-905316 | 19960118 |
| CZ 291556 | B6 | 20030416 | CZ 1997-2340 | 19960118 |
| PT 805796 | T | 20030430 | PT 1996-905316 | 19960118 |
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| SK 283724 | B6 | 20031202 | SK 1997-987 | 19960118 |
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| RO 119885 | B1 | 20050530 | RO 1997-1369 | 19960118 |
| TW 500714 | B | 20020901 | TW 1996-85100690 | 19960122 |
| IL 116846 | A | 20021110 | IL 1996-116846 | 19960122 |
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| NO 320914 | B1 | 20060213 | | |
| FI 9703087 | A | 19970922 | FI 1997-3087 | 19970722 |
| BG 63383 | B1 | 20011231 | BG 1997-101841 | 19970821 |
| US 6376538 | B1 | 20020423 | US 1997-875321 | 19970919 |
| HK 1005241 | A1 | 20030822 | HK 1998-104006 | 19980508 |
| AU 766538 | B2 | 20031016 | AU 2000-62432 | 20001002 |
| US 2003083267 | A1 | 20030501 | US 2001-935461 | 20010822 |
| US 6624152 | B2 | 20030923 | | |
| US 2003018016 | A1 | 20030123 | US 2001-2341 | 20011023 |
| US 6630512 | B2 | 20031007 | | |
| US 7001921 | B1 | 20060221 | US 2003-625626 | 20030724 |
| US 2006166866 | A1 | 20060727 | US 2003-679478 | 20031007 |
| PRIORITY APPLN. INFO.: | | | US 1995-376372 | A2 19950123 |
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| | | | EP 1996-905316 | A3 19960118 |

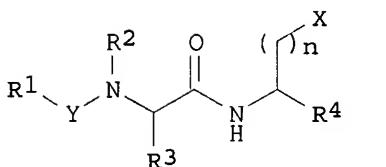
WO 1996-US1349
 US 1997-875321
 US 2001-935461
 US 2001-2341

W 19960118
 A3 19970919
 A1 20010822
 A1 20011023

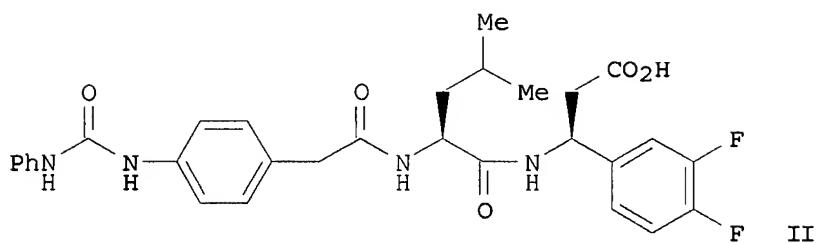
OTHER SOURCE(S) :

MARPAT 125:248489

GI



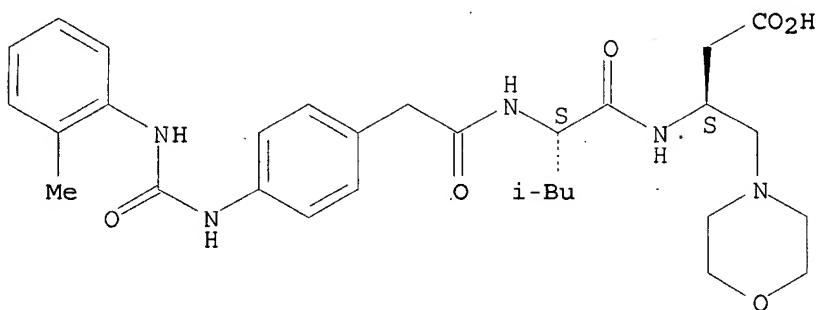
I



II

AB Novel dipeptide analogs I [X = CO₂H, PO₃H-, SO₂R₅, SO₃H, OPO₃H-, CO₂R₄, CONR₄2; Y = CO, SO₂, PO₂; n = 0-2; R₁ = optionally substituted alkyl, alkenyl, alkynyl, aryl-fused cycloalkyl, cycloalkenyl, aryl, aralkyl, aralkenyl, aralkynyl, alkoxy, alkenyloxy, aralkoxy, alkylamino, alkenylamino, alkynylamino, aryloxy, arylamino, N-alkylurea-substituted alkyl, heterocyclyl; R₂ = H, aryl, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, aryl-substituted alkyl; R₂NR₃ = heterocyclic ring; R₃ = natural, unnatural, modified, or substituted amino acid side chain; R₄ = optionally substituted aryl, alkyl, cycloalkyl, alkenyl, cycloalkenyl, alkynyl, aryl-substituted alkyl, H, heterocyclyl, heterocyclylcarbonyl, aminocarbonyl, amido, alkylaminocarbonyl, arylaminocarbonyl, acylaminocarbonyl, acyl; R₅ = alkyl, alkenyl, cycloalkyl, cycloalkenyl, aryl, aralkyl, aralkenyl, aralkynyl] are prepared as compds. useful for inhibition and prevention of cell adhesion and cell adhesion-mediated pathologies. This invention also relates to pharmaceutical formulations comprising these compds. and methods of using them for inhibition and prevention of cell adhesion and cell adhesion-mediated pathologies. The compds. and pharmaceutical compns. of this invention can be used as therapeutic or prophylactic agents. They are particularly well-suited for treatment of many inflammatory and autoimmune diseases. Thus, β -amino acid-containing dipeptide II, prepared by standard methods, displayed an IC₅₀ of <50 nM in a cell adhesion inhibition assay.

IT 181520-66-1P 181520-79-6P 181520-82-1P
 181520-85-4P 181520-90-1P 181520-95-6P
 181521-01-7P 181521-05-1P 181521-13-1P
 181521-26-6P 181521-28-8P 181521-42-6P
 181521-45-9P 181522-35-0P 181522-44-1P
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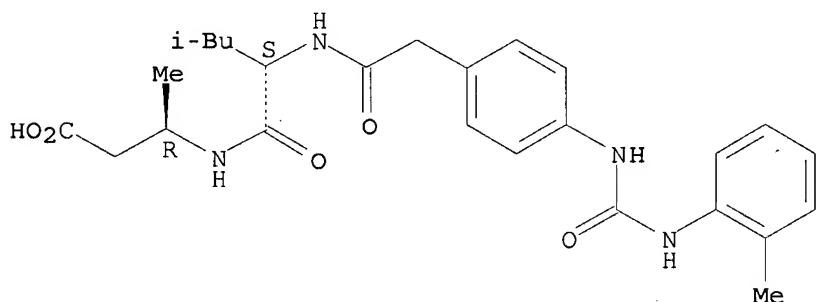
IT 181525-87-1P

RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
 (preparation of β -amino acid dipeptide derivs. as cell adhesion inhibitors)

RN 181525-87-1 CAPLUS

CN Butanoic acid, 3-[(2S)-4-methyl-2-[[4-[[[(2-methylphenyl)amino]carbonyl]amino]phenyl]acetyl]amino]-1-oxopentyl]amino)-(3R)-(9CI) (CA INDEX NAME)

Absolute stereochemistry.



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FILE 'REGISTRY' ENTERED AT 14:13:11 ON 29 NOV 2007

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 L4 STRUCTURE UPLOADED
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L7 26 S L6

=> d l1

L1 HAS NO ANSWERS

L1 STR

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

Structure attributes must be viewed using STN Express query preparation.